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LOGINID:SSSPTA1642BJF

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS	4	MAY 10	CA/CAplus enhanced with 1900-1906 U.S. patent records
NEWS	5	MAY 11	KOREAPAT updates resume
NEWS	6	MAY 19	Derwent World Patents Index to be reloaded and enhanced
NEWS	7	MAY 30	IPC 8 Rolled-up Core codes added to CA/CAplus and USPATFULL/USPAT2
NEWS	8	MAY 30	The F-Term thesaurus is now available in CA/CAplus
NEWS	9	JUN 02	The first reclassification of IPC codes now complete in INPADOC
NEWS	10	JUN 26	TULSA/TULSA2 reloaded and enhanced with new search and and display fields
NEWS	11	JUN 28	Price changes in full-text patent databases EPFULL and PCTFULL
NEWS	12	JUl 11	CHEMSAFE reloaded and enhanced
NEWS	13	JUl 14	FSTA enhanced with Japanese patents
NEWS	14	JUl 19	Coverage of Research Disclosure reinstated in DWPI
NEWS	15	AUG 09	INSPEC enhanced with 1898-1968 archive
NEWS	16	AUG 28	ADISCTI Reloaded and Enhanced
NEWS	17	AUG 30	CA(SM)/CAplus(SM) Austrian patent law changes
NEWS	18	SEP 11	CA/CAplus enhanced with more pre-1907 records
NEWS	19	SEP 21	CA/CAplus fields enhanced with simultaneous left and right truncation
NEWS	20	SEP 25	CA(SM)/CAplus(SM) display of CA Lexicon enhanced
NEWS	21	SEP 25	CAS REGISTRY(SM) no longer includes Concord 3D coordinates
NEWS	22	SEP 25	CAS REGISTRY(SM) updated with amino acid codes for pyrrolysine
NEWS	23	SEP 28	CEABA-VTB classification code fields reloaded with new classification scheme

NEWS EXPRESS	JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS LOGIN	Welcome Banner and News Items
NEWS IPC8	For general information regarding STN implementation of IPC 8
NEWS X25	X.25 communication option no longer available

Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * *

```
FILE 'HOME' ENTERED AT 11:38:17 ON 10 OCT 2006

=> file medline
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILE 'MEDLINE' ENTERED AT 11:38:30 ON 10 OCT 2006

 FILE LAST UPDATED: 7 Oct 2006 (20061007/UP).  FILE COVERS 1950 TO DATE.

 On December 11, 2005, the 2006 MeSH terms were loaded.

 The MEDLINE reload for 2006 is now (26 Feb.) available.  For details
 on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>).
 See also:

    http://www.nlm.nih.gov/mesh/
    http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
    http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

 OLDMEDLINE is covered back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2006 vocabulary.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s BH3 or (LHRH or luteinizing hormone () releasing hormone)
          1173 BH3
          7161 LHRH
             8 LHRHS
          7161 LHRH
                 (LHRH OR LHRHS)
         46441 LUTEINIZING
        282697 HORMONE
        185477 HORMONES
        406408 HORMONE
                 (HORMONE OR HORMONES)
         46180 LUTEINIZING HORMONE
                 (LUTEINIZING(W)HORMONE)
         64153 RELEASING
        282697 HORMONE
        185477 HORMONES
        406408 HORMONE
                 (HORMONE OR HORMONES)
         43288 RELEASING HORMONE
                 (RELEASING(W)HORMONE)
          4581 LUTEINIZING HORMONE (W) RELEASING HORMONE
L1       10594 BH3 OR (LHRH OR LUTEINIZING HORMONE (W) RELEASING HORMONE)

=> s cancer? or neoplas? or tumor?
        587390 CANCER?
       1524536 NEOPLAS?
        814539 TUMOR?
L2     1850590 CANCER? OR NEOPLAS? OR TUMOR?

=> s l2 and l1
L3        2438 L2 AND L1

=> s target? or transport? or homing or home
```

```
         352506 TARGET?
         326217 TRANSPORT?
           7013 HOMING
         103834 HOME
          36597 HOMES
         127224 HOME
                  (HOME OR HOMES)
L4       787167 TARGET? OR TRANSPORT? OR HOMING OR HOME

=> s l4 and l3
L5          321 L4 AND L3

=> s conjugat? or link? or coupl?
          82886 CONJUGAT?
         430336 LINK?
         174363 COUPL?
L6       658920 CONJUGAT? OR LINK? OR COUPL?

=> s l6 and l5
L7           92 L6 AND L5

=> s l7 and (PEG or (poly () ethylene glycol))
          10609 PEG
            810 PEGS
          11023 PEG
                  (PEG OR PEGS)
          65419 POLY
              6 POLIES
          65425 POLY
                  (POLY OR POLIES)
          21260 ETHYLENE
           2542 ETHYLENES
          21971 ETHYLENE
                  (ETHYLENE OR ETHYLENES)
          24566 GLYCOL
          29764 GLYCOLS
          43515 GLYCOL
                  (GLYCOL OR GLYCOLS)
           9444 ETHYLENE GLYCOL
                  (ETHYLENE(W)GLYCOL)
           3022 POLY (W) ETHYLENE GLYCOL
L8            2 L7 AND (PEG OR (POLY (W) ETHYLENE GLYCOL))

=> d ibib 1-2

L8   ANSWER 1 OF 2     MEDLINE on STN
ACCESSION NUMBER:    2006108984     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 16291730
TITLE:               Molecular targeting of BCL2 and BCLXL proteins by
                     synthetic BCL2 homology 3 domain peptide enhances the
                     efficacy of chemotherapy.
AUTHOR:              Dharap Sonia S; Chandna Pooja; Wang Yang; Khandare Jayant
                     J; Qiu Bo; Stein Stanley; Minko Tamara
CORPORATE SOURCE:    Department of Pharmaceutics, Rutgers, The State University
                     of New Jersey, 160 Frelinghuysen Road, Piscataway, NJ
                     08854-8020, USA.
CONTRACT NUMBER:     CA100098 (NCI)
SOURCE:              The Journal of pharmacology and experimental therapeutics,
                     (2006 Mar) Vol. 316, No. 3, pp. 992-8.  Electronic
                     Publication: 2005-11-15.
                     Journal code: 0376362. ISSN: 0022-3565.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
```

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FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200604
ENTRY DATE:         Entered STN: 28 Feb 2006
                    Last Updated on STN: 14 Apr 2006
                    Entered Medline: 13 Apr 2006

L8   ANSWER 2 OF 2     MEDLINE on STN
ACCESSION NUMBER:   2003395988     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12932638
TITLE:              Molecular targeting of drug delivery systems to
                    ovarian cancer by BH3 and LHRH
                    peptides.
AUTHOR:             Dharap S S; Qiu B; Williams G C; Sinko P; Stein S; Minko T
CORPORATE SOURCE:   Department of Pharmaceutics, Rutgers, The State University
                    of New Jersey, 160 Frelinghuysen Road, Piscataway, NJ
                    08854-8020, USA.
SOURCE:             Journal of controlled release : official journal of the
                    Controlled Release Society, (2003 Aug 28) Vol. 91, No. 1-2,
                    pp. 61-73.
                    Journal code: 8607908. ISSN: 0168-3659.
PUB. COUNTRY:       Netherlands
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        200310
ENTRY DATE:         Entered STN: 23 Aug 2003
                    Last Updated on STN: 16 Oct 2003
                    Entered Medline: 15 Oct 2003


=> d his

     (FILE 'HOME' ENTERED AT 11:38:17 ON 10 OCT 2006)

     FILE 'MEDLINE' ENTERED AT 11:38:30 ON 10 OCT 2006
L1         10594 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
L2       1850590 S CANCER? OR NEOPLAS? OR TUMOR?
L3          2438 S L2 AND L1
L4        787167 S TARGET? OR TRANSPORT? OR HOMING OR HOME
L5           321 S L4 AND L3
L6        658920 S CONJUGAT? OR LINK? OR COUPL?
L7            92 S L6 AND L5
L8             2 S L7 AND (PEG OR (POLY () ETHYLENE GLYCOL))

=> s l7 not py>2002
       2305530 PY>2002
                  (PY>20029999)
L9            46 L7 NOT PY>2002

=> s l7 not py>2001
       2848768 PY>2001
                 (PY>20019999)
L10           37 L7 NOT PY>2001

=> d ibib

L10  ANSWER 1 OF 37     MEDLINE on STN
ACCESSION NUMBER:   2003161938     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 12678771
TITLE:              Peptides as carrier for tumor diagnosis and
                    treatment.
AUTHOR:             Langer M; Beck-Sickinger A G
CORPORATE SOURCE:   Institute of Biochemistry, University of Leipzig, Germany.
SOURCE:             Current medicinal chemistry. Anti-cancer agents, (2001 May)
```

Vol. 1, No. 1, pp. 71-93. Ref: 240
Journal code: 101123597. ISSN: 1568-0118.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 8 Apr 2003
Last Updated on STN: 30 Apr 2003
Entered Medline: 29 Apr 2003

=> d kwic

L10 ANSWER 1 OF 37 MEDLINE on STN
TI Peptides as carrier for tumor diagnosis and treatment.
AB The specific binding of peptides to their receptors can be used to meet the key requirement in tumor targeting: selective addressing of neoplasm. Because of their small size, peptides exhibit faster blood clearance and higher target-to-background ratios compared to macromolecular compounds. In radiopharmacy, these advantages have been attended, and radiolabelled receptor-binding peptides have emerged as a new class of radiopharmaceuticals. Over the last years, nuclear medicine has evaluated various peptides for tumor scintigraphy. The challenge is to label bioactive peptides without affecting their receptor binding properties. Size, plasma protein binding, lipophilicity and. . . peptide analogues and radiolabelling methods, and latest results from in vitro, in vivo and clinical studies will be presented. The tumor receptor-targeting approach with peptides can be extended to cancer chemotherapy. One of the major problems in classic chemotherapy is the non-specific toxicity of most anticancer agents against normal cells. Coupling cytotoxic drugs to macromolecular carriers has been shown to be a promising approach for efficient drug targeting. In the past few years, peptides were introduced as carriers. Different conjugates, composed of a peptide carrier and a cytotoxic moiety, have been investigated so far. Anticancer drugs were coupled to analogues of luteinizing hormone-releasing hormone, bombesin, somatostatin and neuropeptide Y. Suitable candidates maintained their binding affinity and could preserve the cytotoxic activity in vitro and. . .
CT Animals
*Antineoplastic Agents: AD, administration & dosage
*Drug Carriers
Drug Design
Humans
*Neoplasms: DI, diagnosis
*Neoplasms: DT, drug therapy
Neoplasms: ME, metabolism
*Peptides: AD, administration & dosage
Radiopharmaceuticals
Receptors, Cell Surface: ME, metabolism

=> d ibib 2

L10 ANSWER 2 OF 37 MEDLINE on STN
ACCESSION NUMBER: 2002010552 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11353532
TITLE: Synthesis, characterization, and labeling with 99mTc/188Re of peptide conjugates containing a dithia-bisphosphine chelating agent.
AUTHOR: Gali H; Hoffman T J; Sieckman G L; Owen N K; Katti K V;

Volkert W A
CORPORATE SOURCE: Department of Radiology, University of Missouri-Columbia, Columbia, Missouri 65211, USA.
CONTRACT NUMBER: CA72942 (NCI)
SOURCE: Bioconjugate chemistry, (2001 May-Jun) Vol. 12, No. 3, pp. 354-63.
Journal code: 9010319. ISSN: 1043-1802.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 21 Jan 2002
Last Updated on STN: 21 Jan 2002
Entered Medline: 4 Dec 2001

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	4.63	4.84

FILE 'CAPLUS' ENTERED AT 11:44:31 ON 10 OCT 2006

FILE COVERS 1907 - 10 Oct 2006 VOL 145 ISS 16
FILE LAST UPDATED: 8 Oct 2006 (20061008/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.
They are available for your review at:

http://www.cas.org/infopolicy.html

=> s BH3 or (LHRH or luteinizing hormone () releasing hormone)
4958 BH3
11593 LHRH
3 LHRHS
11593 LHRH
(LHRH OR LHRHS)
14890 LUTEINIZING
281272 HORMONE
213595 HORMONES
391232 HORMONE
(HORMONE OR HORMONES)
14255 LUTEINIZING HORMONE
(LUTEINIZING(W)HORMONE)
58250 LH
239 LHS
58451 LH
(LH OR LHS)
60167 LUTEINIZING HORMONE

```
                (LUTEINIZING HORMONE OR LH)
         91102 RELEASING
             1 RELEASINGS
         91102 RELEASING
                (RELEASING OR RELEASINGS)
        281272 HORMONE
        213595 HORMONES
        391232 HORMONE
                (HORMONE OR HORMONES)
         27788 RELEASING HORMONE
                (RELEASING(W)HORMONE)
          5162 LUTEINIZING HORMONE (W) RELEASING HORMONE
L11       18828 BH3 OR (LHRH OR LUTEINIZING HORMONE (W) RELEASING HORMONE)

=> s cancer? or neoplas? or tumor?
        308038 CANCER?
        465841 NEOPLAS?
        443727 TUMOR?
L12     735161 CANCER? OR NEOPLAS? OR TUMOR?

=> s target? or transport? or homing or home
        493116 TARGET?
        797498 TRANSPORT?
          4693 HOMING
         18529 HOME
          3502 HOMES
         21141 HOME
                (HOME OR HOMES)
L13    1280700 TARGET? OR TRANSPORT? OR HOMING OR HOME

=> s conjugat? or link? or coupl?
        227042 CONJUGAT?
        470685 LINK?
        789666 COUPL?
L14    1422867 CONJUGAT? OR LINK? OR COUPL?

=> s l7 and (PEG or (poly () ethylene glycol))
        227042 CONJUGAT?
        470685 LINK?
        789666 COUPL?
        493116 TARGET?
        797498 TRANSPORT?
          4693 HOMING
         18529 HOME
          3502 HOMES
         21141 HOME
                (HOME OR HOMES)
        308038 CANCER?
        465841 NEOPLAS?
        443727 TUMOR?
          4958 BH3
         11593 LHRH
             3 LHRHS
         11593 LHRH
                (LHRH OR LHRHS)
         14890 LUTEINIZING
        281272 HORMONE
        213595 HORMONES
        391232 HORMONE
                (HORMONE OR HORMONES)
         14255 LUTEINIZING HORMONE
                (LUTEINIZING(W)HORMONE)
         58250 LH
           239 LHS
```

```
         58451 LH
                 (LH OR LHS)
         60167 LUTEINIZING HORMONE
                 (LUTEINIZING HORMONE OR LH)
         91102 RELEASING
             1 RELEASINGS
         91102 RELEASING
                 (RELEASING OR RELEASINGS)
        281272 HORMONE
        213595 HORMONES
        391232 HORMONE
                 (HORMONE OR HORMONES)
         27788 RELEASING HORMONE
                 (RELEASING(W)HORMONE)
          5162 LUTEINIZING HORMONE (W) RELEASING HORMONE
         37631 PEG
          1252 PEGS
         38151 PEG
                 (PEG OR PEGS)
        680795 POLY
             2 POLIES
        680796 POLY
                 (POLY OR POLIES)
        532239 ETHYLENE
          3370 ETHYLENES
        533723 ETHYLENE
                 (ETHYLENE OR ETHYLENES)
        357383 GLYCOL
         45703 GLYCOLS
        373063 GLYCOL
                 (GLYCOL OR GLYCOLS)
        130628 ETHYLENE GLYCOL
                 (ETHYLENE(W)GLYCOL)
         14861 POLY (W) ETHYLENE GLYCOL
L15          6 L7 AND (PEG OR (POLY (W) ETHYLENE GLYCOL))

=> s (PEG or (poly () ethylene glycol))
         37631 PEG
          1252 PEGS
         38151 PEG
                 (PEG OR PEGS)
        680795 POLY
             2 POLIES
        680796 POLY
                 (POLY OR POLIES)
        532239 ETHYLENE
          3370 ETHYLENES
        533723 ETHYLENE
                 (ETHYLENE OR ETHYLENES)
        357383 GLYCOL
         45703 GLYCOLS
        373063 GLYCOL
                 (GLYCOL OR GLYCOLS)
        130628 ETHYLENE GLYCOL
                 (ETHYLENE(W)GLYCOL)
         14861 POLY (W) ETHYLENE GLYCOL
L16      47211 (PEG OR (POLY (W) ETHYLENE GLYCOL))

=> d his

     (FILE 'HOME' ENTERED AT 11:38:17 ON 10 OCT 2006)

     FILE 'MEDLINE' ENTERED AT 11:38:30 ON 10 OCT 2006
L1        10594 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
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L2      1850590 S CANCER? OR NEOPLAS? OR TUMOR?
L3         2438 S L2 AND L1
L4       787167 S TARGET? OR TRANSPORT? OR HOMING OR HOME
L5          321 S L4 AND L3
L6       658920 S CONJUGAT? OR LINK? OR COUPL?
L7           92 S L6 AND L5
L8            2 S L7 AND (PEG OR (POLY () ETHYLENE GLYCOL))
L9           46 S L7 NOT PY>2002
L10          37 S L7 NOT PY>2001

     FILE 'CAPLUS' ENTERED AT 11:44:31 ON 10 OCT 2006
L11       18828 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
L12      735161 S CANCER? OR NEOPLAS? OR TUMOR?
L13     1280700 S TARGET? OR TRANSPORT? OR HOMING OR HOME
L14     1422867 S CONJUGAT? OR LINK? OR COUPL?
L15           6 S L7 AND (PEG OR (POLY () ETHYLENE GLYCOL))
L16       47211 S (PEG OR (POLY () ETHYLENE GLYCOL))

=> s l17 and l11
L17 NOT FOUND
The L-number entered could not be found.  To see the definition
of L-numbers, enter DISPLAY HISTORY at an arrow prompt (=>).

=> s l16 and l11
L17          47 L16 AND L11

=> s l17 and l12
L18          19 L17 AND L12

=> s l18 and l13
L19           7 L18 AND L13

=> s l19 not py>2002
       4430382 PY>2002
L20           0 L19 NOT PY>2002

=> s l19 not py>2003
       3369746 PY>2003
L21           1 L19 NOT PY>2003

=> d ibib

L21  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2003:640770  CAPLUS
DOCUMENT NUMBER:          140:240730
TITLE:                    Molecular targeting of drug delivery systems
                          to ovarian cancer by BH3 and LH-RH
                          peptides
AUTHOR(S):                Dharap, S. S.; Qiu, B.; Williams, G. C.; Sinko, P.;
                          Stein, S.; Minko, T.
CORPORATE SOURCE:         Department of Pharmaceutics, Rutgers, The State
                          University of New Jersey, Piscataway, NJ, 08854-8020,
                          USA
SOURCE:                   Journal of Controlled Release (2003), 91(1-2), 61-73
                          CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER:                Elsevier Science Ltd.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          38    THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> s doxorubicin
         15448 DOXORUBICIN
```

```
            28 DOXORUBICINS
L22      15450 DOXORUBICIN
                (DOXORUBICIN OR DOXORUBICINS)

=> s l22 (L) l16
L23        256 L22 (L) L16

=> s l23 and l13
L24        118 L23 AND L13

=> s l24 and l11
L25          0 L24 AND L11

=> s l24 not py>2001
       5408230 PY>2001
L26         52 L24 NOT PY>2001

=> d ibib 1-2

L26  ANSWER 1 OF 52  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2001:856893  CAPLUS
DOCUMENT NUMBER:          137:129662
TITLE:                    Targeted delivery and triggered release of
                          liposomal doxorubicin enhances cytotoxicity against
                          human B lymphoma cells
AUTHOR(S):                Ishida, T.; Kirchmeier, M. J.; Moase, E. H.; Zalipsky,
                          S.; Allen, T. M.
CORPORATE SOURCE:         Department of Pharmacology, University of Alberta,
                          Edmonton, AB, T6G 2H7, Can.
SOURCE:                   Biochimica et Biophysica Acta, Biomembranes (2001),
                          1515(2), 144-158
                          CODEN: BBBMBS; ISSN: 0005-2736
PUBLISHER:                Elsevier B.V.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
REFERENCE COUNT:          40    THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26  ANSWER 2 OF 52  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2001:770894  CAPLUS
DOCUMENT NUMBER:          137:10788
TITLE:                    Development of artificial viral vector for gene
                          therapy. Approach from polymer nanotechnology
AUTHOR(S):                Kataoka, Kazunori
CORPORATE SOURCE:         Dep. Materials Sci., Univ. Tokyo, Bunkyo-ku, Tokyo,
                          113-8656, Japan
SOURCE:                   Biotherapy (Tokyo, Japan) (2001), 15(4), 425-431
                          CODEN: BITPE9; ISSN: 0914-2223
PUBLISHER:                Gan to Kagaku Ryohosha
DOCUMENT TYPE:            Journal; General Review
LANGUAGE:                 Japanese


=> d ibib 3-4

L26  ANSWER 3 OF 52  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:         2001:590401  CAPLUS
DOCUMENT NUMBER:          135:352443
TITLE:                    Immunoprotective therapy with targeted
                          anticancer drugs
AUTHOR(S):                Rihova, B.; Strohalm, J.; Hoste, K.; Jelinkova, M.;
                          Hovorka, O.; Kovar, M.; Plocova, D.; Sirova, M.;
                          St'astny, M.; Schacht, E.; Ulbrich, K.
CORPORATE SOURCE:         Institute of Microbiology, Academy of Sciences of the
```

Czech Republic, Prague, 142 20/4, Czech Rep.
SOURCE: Macromolecular Symposia (2001), 172(Polymers in Medicine), 21-28
CODEN: MSYMEC; ISSN: 1022-1360
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 4 OF 52 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:572410 CAPLUS
DOCUMENT NUMBER: 136:267971
TITLE: Polymer-drug conjugates, polymer-directed enzyme prodrug therapy (PDEPT) and (polymer-enzyme liposome therapy) PELT: basic principles for design and transfer from the laboratory to clinic
AUTHOR(S): Duncan, R.; Gac-Breton, S.; Keane, R.; Musila, R.; Sat, Y. N.; Satchi, R.; Searle, F.
CORPORATE SOURCE: Centre for Polymer Therapeutics, Welsh School of Pharmacy, Cardiff University, Cardiff, CF10 3XF, UK
SOURCE: Journal of Controlled Release (2001), 74(1-3), 135-146
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 11:38:17 ON 10 OCT 2006)

FILE 'MEDLINE' ENTERED AT 11:38:30 ON 10 OCT 2006
L1 10594 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
L2 1850590 S CANCER? OR NEOPLAS? OR TUMOR?
L3 2438 S L2 AND L1
L4 787167 S TARGET? OR TRANSPORT? OR HOMING OR HOME
L5 321 S L4 AND L3
L6 658920 S CONJUGAT? OR LINK? OR COUPL?
L7 92 S L6 AND L5
L8 2 S L7 AND (PEG OR (POLY () ETHYLENE GLYCOL))
L9 46 S L7 NOT PY>2002
L10 37 S L7 NOT PY>2001

FILE 'CAPLUS' ENTERED AT 11:44:31 ON 10 OCT 2006
L11 18828 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
L12 735161 S CANCER? OR NEOPLAS? OR TUMOR?
L13 1280700 S TARGET? OR TRANSPORT? OR HOMING OR HOME
L14 1422867 S CONJUGAT? OR LINK? OR COUPL?
L15 6 S L7 AND (PEG OR (POLY () ETHYLENE GLYCOL))
L16 47211 S (PEG OR (POLY () ETHYLENE GLYCOL))
L17 47 S L16 AND L11
L18 19 S L17 AND L12
L19 7 S L18 AND L13
L20 0 S L19 NOT PY>2002
L21 1 S L19 NOT PY>2003
L22 15450 S DOXORUBICIN
L23 256 S L22 (L) L16
L24 118 S L23 AND L13
L25 0 S L24 AND L11
L26 52 S L24 NOT PY>2001

```
=> s l26/pat
QUALIFICATION NOT VALID FOR NUMERIC DATA 'PY/PAT'
Numeric data cannot be field qualified.

=> s l26/pn
QUALIFICATION NOT VALID FOR NUMERIC DATA 'PY/PN'
Numeric data cannot be field qualified.

=> file pctfull
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                        ENTRY    SESSION
FULL ESTIMATED COST                                     95.18     100.02

FILE 'PCTFULL' ENTERED AT 11:49:06 ON 10 OCT 2006
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FILE LAST UPDATED:          10 OCT 2006      <20061010/UP>
MOST RECENT UPDATE WEEK:       200640         <200640/EW>
FILE COVERS 1978 TO DATE

>>> IMAGES ARE AVAILABLE ONLINE AND FOR EMAIL-PRINTS <<<

>>> NEW IPC8 DATA AND FUNCTIONALITY NOW AVAILABLE IN THIS FILE.
    SEE
    http://www.stn-international.de/stndatabases/details/ipc-reform.html >>>

>>> FOR CHANGES IN PCTFULL PLEASE SEE HELP CHANGE
    (last updated April 10, 2006) <<<

>>> NEW PRICES IN PCTFULL AS OF 01 JULY 2006. FOR DETAILS,
    PLEASE SEE HELP COST <<<

=> s BH3 or (LHRH or luteinizing hormone () releasing hormone)
          3189 BH3
          2629 LHRH
             2 LHRHS
          2629 LHRH
                 (LHRH OR LHRHS)
          3374 LUTEINIZING
         40271 HORMONE
         33241 HORMONES
         54507 HORMONE
                 (HORMONE OR HORMONES)
          3166 LUTEINIZING HORMONE
                 (LUTEINIZING(W)HORMONE)
         63893 RELEASING
             3 RELEASINGS
         63896 RELEASING
                 (RELEASING OR RELEASINGS)
         40271 HORMONE
         33241 HORMONES
         54507 HORMONE
                 (HORMONE OR HORMONES)
          4897 RELEASING HORMONE
                 (RELEASING(W)HORMONE)
          1048 LUTEINIZING HORMONE (W) RELEASING HORMONE
L27       6069 BH3 OR (LHRH OR LUTEINIZING HORMONE (W) RELEASING HORMONE)

=> s cancer? or neoplas? or tumor?
         82122 CANCER?
         23825 NEOPLAS?
         68474 TUMOR?
L28     102117 CANCER? OR NEOPLAS? OR TUMOR?
```

```
=> s target? or transport? or homing or home
        186329 TARGET?
        221757 TRANSPORT?
          3225 HOMING
             4 HOMINGS
          3227 HOMING
                 (HOMING OR HOMINGS)
         57729 HOME
          8751 HOMES
         62048 HOME
                 (HOME OR HOMES)
L29     382854 TARGET? OR TRANSPORT? OR HOMING OR HOME

=> s conjugat? or link? or coupl?
         78988 CONJUGAT?
        313809 LINK?
        347075 COUPL?
L30     530007 CONJUGAT? OR LINK? OR COUPL?

=> s (PEG or (poly () ethylene glycol))
         39048 PEG
          5499 PEGS
         41356 PEG
                 (PEG OR PEGS)
        122572 POLY
           313 POLIES
        122862 POLY
                 (POLY OR POLIES)
        108845 ETHYLENE
           538 ETHYLENES
        108938 ETHYLENE
                 (ETHYLENE OR ETHYLENES)
        114877 GLYCOL
         45189 GLYCOLS
        122430 GLYCOL
                 (GLYCOL OR GLYCOLS)
         40280 ETHYLENE GLYCOL
                 (ETHYLENE(W)GLYCOL)
          6433 POLY (W) ETHYLENE GLYCOL
L31      44564 (PEG OR (POLY (W) ETHYLENE GLYCOL))

=> d his

     (FILE 'HOME' ENTERED AT 11:38:17 ON 10 OCT 2006)

     FILE 'MEDLINE' ENTERED AT 11:38:30 ON 10 OCT 2006
L1       10594 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
L2     1850590 S CANCER? OR NEOPLAS? OR TUMOR?
L3        2438 S L2 AND L1
L4      787167 S TARGET? OR TRANSPORT? OR HOMING OR HOME
L5         321 S L4 AND L3
L6      658920 S CONJUGAT? OR LINK? OR COUPL?
L7          92 S L6 AND L5
L8           2 S L7 AND (PEG OR (POLY () ETHYLENE GLYCOL))
L9          46 S L7 NOT PY>2002
L10         37 S L7 NOT PY>2001

     FILE 'CAPLUS' ENTERED AT 11:44:31 ON 10 OCT 2006
L11      18828 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
L12     735161 S CANCER? OR NEOPLAS? OR TUMOR?
L13    1280700 S TARGET? OR TRANSPORT? OR HOMING OR HOME
L14    1422867 S CONJUGAT? OR LINK? OR COUPL?
L15          6 S L7 AND (PEG OR (POLY () ETHYLENE GLYCOL))
L16      47211 S (PEG OR (POLY () ETHYLENE GLYCOL))
```

```
L17           47 S L16 AND L11
L18           19 S L17 AND L12
L19            7 S L18 AND L13
L20            0 S L19 NOT PY>2002
L21            1 S L19 NOT PY>2003
L22        15450 S DOXORUBICIN
L23          256 S L22 (L) L16
L24          118 S L23 AND L13
L25            0 S L24 AND L11
L26           52 S L24 NOT PY>2001

     FILE 'PCTFULL' ENTERED AT 11:49:06 ON 10 OCT 2006
L27         6069 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
L28       102117 S CANCER? OR NEOPLAS? OR TUMOR?
L29       382854 S TARGET? OR TRANSPORT? OR HOMING OR HOME
L30       530007 S CONJUGAT? OR LINK? OR COUPL?
L31        44564 S (PEG OR (POLY () ETHYLENE GLYCOL))

=> s l27 and l28
L32        4089 L27 AND L28

=> s l32 and l29
L33        3135 L32 AND L29

=> s l33 and l3
          82122 CANCER?
          23825 NEOPLAS?
          68474 TUMOR?
           3189 BH3
           2629 LHRH
              2 LHRHS
           2629 LHRH
                  (LHRH OR LHRHS)
           3374 LUTEINIZING
          40271 HORMONE
          33241 HORMONES
          54507 HORMONE
                  (HORMONE OR HORMONES)
           3166 LUTEINIZING HORMONE
                  (LUTEINIZING(W)HORMONE)
          63893 RELEASING
              3 RELEASINGS
          63896 RELEASING
                  (RELEASING OR RELEASINGS)
          40271 HORMONE
          33241 HORMONES
          54507 HORMONE
                  (HORMONE OR HORMONES)
           4897 RELEASING HORMONE
                  (RELEASING(W)HORMONE)
           1048 LUTEINIZING HORMONE (W) RELEASING HORMONE
L34        3135 L33 AND L3

=> s l33 and l30
L35        2910 L33 AND L30

=> s l35 and l31
L36         907 L35 AND L31

=> s l36 and dox
           1343 DOX
              2 DOXES
           1345 DOX
                  (DOX OR DOXES)
```

```
L37         27 L36 AND DOX

=> s l36 and dox?
         18023 DOX?
L38        454 L36 AND DOX?

=> s l38 not py>2001
        557288 PY>2001
L39         95 L38 NOT PY>2001

=> d his

     (FILE 'HOME' ENTERED AT 11:38:17 ON 10 OCT 2006)

     FILE 'MEDLINE' ENTERED AT 11:38:30 ON 10 OCT 2006
L1       10594 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
L2     1850590 S CANCER? OR NEOPLAS? OR TUMOR?
L3        2438 S L2 AND L1
L4      787167 S TARGET? OR TRANSPORT? OR HOMING OR HOME
L5         321 S L4 AND L3
L6      658920 S CONJUGAT? OR LINK? OR COUPL?
L7          92 S L6 AND L5
L8           2 S L7 AND (PEG OR (POLY () ETHYLENE GLYCOL))
L9          46 S L7 NOT PY>2002
L10         37 S L7 NOT PY>2001

     FILE 'CAPLUS' ENTERED AT 11:44:31 ON 10 OCT 2006
L11      18828 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
L12     735161 S CANCER? OR NEOPLAS? OR TUMOR?
L13    1280700 S TARGET? OR TRANSPORT? OR HOMING OR HOME
L14    1422867 S CONJUGAT? OR LINK? OR COUPL?
L15          6 S L7 AND (PEG OR (POLY () ETHYLENE GLYCOL))
L16      47211 S (PEG OR (POLY () ETHYLENE GLYCOL))
L17         47 S L16 AND L11
L18         19 S L17 AND L12
L19          7 S L18 AND L13
L20          0 S L19 NOT PY>2002
L21          1 S L19 NOT PY>2003
L22      15450 S DOXORUBICIN
L23        256 S L22 (L) L16
L24        118 S L23 AND L13
L25          0 S L24 AND L11
L26         52 S L24 NOT PY>2001

     FILE 'PCTFULL' ENTERED AT 11:49:06 ON 10 OCT 2006
L27       6069 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
L28     102117 S CANCER? OR NEOPLAS? OR TUMOR?
L29     382854 S TARGET? OR TRANSPORT? OR HOMING OR HOME
L30     530007 S CONJUGAT? OR LINK? OR COUPL?
L31      44564 S (PEG OR (POLY () ETHYLENE GLYCOL))
L32       4089 S L27 AND L28
L33       3135 S L32 AND L29
L34       3135 S L33 AND L3
L35       2910 S L33 AND L30
L36        907 S L35 AND L31
L37         27 S L36 AND DOX
L38        454 S L36 AND DOX?
L39         95 S L38 NOT PY>2001

=> s l27/ab
           18 BH3/AB
           90 LHRH/AB
           58 LUTEINIZING/AB
         2244 HORMONE/AB
```

```
          857 HORMONES/AB
         2609 HORMONE/AB
                ((HORMONE OR HORMONES)/AB)
           56 LUTEINIZING HORMONE/AB
                ((LUTEINIZING(W)HORMONE)/AB)
         5441 RELEASING/AB
         2244 HORMONE/AB
          857 HORMONES/AB
         2609 HORMONE/AB
                ((HORMONE OR HORMONES)/AB)
          179 RELEASING HORMONE/AB
                ((RELEASING(W)HORMONE)/AB)
           21 LUTEINIZING HORMONE/AB (W) RELEASING HORMONE/AB
L40       121 (BH3/AB OR (LHRH/AB OR LUTEINIZING HORMONE/AB (W) RELEASING
              HORMONE/AB))

=> s l27/clm
          278 BH3/CLM
          393 LHRH/CLM
          386 LUTEINIZING/CLM
         7145 HORMONE/CLM
          361 LUTEINIZING HORMONE/CLM
                ((LUTEINIZING(W)HORMONE)/CLM)
        16428 RELEASING/CLM
         7145 HORMONE/CLM
          711 RELEASING HORMONE/CLM
                ((RELEASING(W)HORMONE)/CLM)
          159 LUTEINIZING HORMONE/CLM (W) RELEASING HORMONE/CLM
L41       762 (BH3/CLM OR (LHRH/CLM OR LUTEINIZING HORMONE/CLM (W) RELEASING
              HORMONE/CLM))

=> s l41 or l40
L42       789 L41 OR L40

=> s l42 and l39
L43         8 L42 AND L39

=> d ibib 1-4

L43    ANSWER 1 OF 8     PCTFULL   COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER:        2001091798 PCTFULL  ED 20020826
TITLE (ENGLISH):         TUMOR ACTIVATED PRODRUG COMPOUNDS AND METHODS
                         OF MAKING AND USING THE SAME
TITLE (FRENCH):          COMPOSES DE PROMEDICAMENTS A ACTIVATION
                         TUMORALE ET PROCEDES DE FABRICATION ET
                         D'UTILISATION DE CES DERNIERS
INVENTOR(S):             TROUET, Andre;
                         DUBOIS, Vincent;
                         ORONSKY, Arnold
PATENT ASSIGNEE(S):      UNIVERSITE CATHOLIQUE DE LOUVAIN;
                         TROUET, Andre;
                         DUBOIS, Vincent;
                         ORONSKY, Arnold
DOCUMENT TYPE:           Patent
PATENT INFORMATION:
                         NUMBER              KIND     DATE
                         ---------------------------------
                         WO 2001091798        A2 20011206
DESIGNATED STATES
       W:                AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU
                         CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN
                         IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK
                         MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM
                         TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD
```

SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY
DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR BF BJ CF
CG CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2001-EP6106 A 20010529
PRIORITY INFO.: US 2000-60/208,996 20000601
EP 2000-00870130.2 20000615
EP 2000-00870306.8 20001218

L43 ANSWER 2 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2001028524 PCTFULL ED 20020820
TITLE (ENGLISH): SUSTAINED RELEASE MICROSPHERES
TITLE (FRENCH): MICROSPHERES A LIBERATION PROLONGEE
INVENTOR(S): SCOTT, Terrence, L.;
BROWN, Larry, R.;
RISKE, Frank, J.;
BLIZZARD, Charles, D.;
RASHBA-STEP, Julia
PATENT ASSIGNEE(S): EPIC THERAPEUTICS, INC.;
SCOTT, Terrence, L.;
BROWN, Larry, R.;
RISKE, Frank, J.;
BLIZZARD, Charles, D.;
RASHBA-STEP, Julia
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001028524	A1	20010426

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU
CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN
IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK
MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM
TR TT TZ UA UG US UZ VN YU ZA ZW GH GM KE LS MW MZ SD
SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY
DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG
CI CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US28200 A 20001012
PRIORITY INFO.: US 1999-09/420,361 19991018

L43 ANSWER 3 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2001017543 PCTFULL ED 20020828
TITLE (ENGLISH): COMPOSITIONS AND METHODS FOR THE PREVENTION OR
TREATMENT OF CANCER AND BONE LOSS ASSOCIATED
WITH CANCER
TITLE (FRENCH): COMPOSITIONS ET PROCEDES PERMETTANT LA PREVENTION OU LE
TRAITEMENT DU CANCER ET DE LA PERTE OSSEUSE
ASSOCIEE AU CANCER
INVENTOR(S): DUNSTAN, Colin, R.
PATENT ASSIGNEE(S): AMGEN INC.
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2001017543	A2	20010315

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU
CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN
IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK
MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM
TR TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW MZ SD SL
SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE
DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI
CM GA GN GW ML MR NE SN TD TG

APPLICATION INFO.: WO 2000-US22806 A 20000818
PRIORITY INFO.: US 1999-09/389,545 19990903

L43 ANSWER 4 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 2000066085 PCTFULL ED 20020515
TITLE (ENGLISH): A BIOACTIVE AGENT DELIVERING SYSTEM COMPRISED OF MICROPARTICLES WITHIN A BIODEGRADABLE TO IMPROVE RELEASE PROFILES
TITLE (FRENCH): SYSTEME D'APPORT POUR AGENT BIOACTIF CONSTITUE DE MICROPARTICULES PRISES DANS UN MATERIAU BIODEGRADABLE DESTINE A AMELIORER LES PROFILS DE LIBERATION
INVENTOR(S): SHIH, Chung;
ZENTNER, Gaylen, M.
PATENT ASSIGNEE(S): MACROMED, INC.
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 2000066085	A1	20001109

DESIGNATED STATES
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW GH GM KE LS MW SD SL SZ TZ UG ZW AM AZ BY KG KZ MD RU TJ TM AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG
APPLICATION INFO.: WO 2000-US11387 A 20000428
PRIORITY INFO.: US 1999-60/131,562 19990429
US 2000-09/559,507 20000427

=> d ibib 5-8

L43 ANSWER 5 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1997032604 PCTFULL ED 20020514
TITLE (ENGLISH): ANTIPROLIFERATIVE COMBINATIONS, CONTAINING RAF-TARGETED OLIGONUCLEOTIDES AND CHEMOTHERAPEUTIC COMPOUNDS
TITLE (FRENCH): COMBINAISONS ANTIPROLIFERATIVES CONTENANT DES OLIGONUCLEOTIDES CIBLES SUR RAF ET DES COMPOSES CHIMIOTHERAPEUTIQUES
INVENTOR(S): MueLLER, Marcel;
GEIGER, Thomas;
ALTMANN, Karl-Heinz;
FABBRO, Doriano;
MONIA, Brett
PATENT ASSIGNEE(S): NOVARTIS AG
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9732604	A1	19970912

DESIGNATED STATES
W: AL AU BA BB BG BR CA CN CU CZ EE GE HU IL IS JP KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO SG SI SK TR TT UA UZ VN YU KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.: WO 1997-EP875 A 19970224
PRIORITY INFO.: US 1996-8/612,787 19960307

L43 ANSWER 6 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1997032589 PCTFULL ED 20020514
TITLE (ENGLISH): COMBINATIONS FOR TREATMENT OF PROLIFERATIVE DISEASES
TITLE (FRENCH): COMBINAISONS DESTINEES AU TRAITEMENT DE MALADIES PROLIFERATIVES
INVENTOR(S): MueLLER, Marcel;
GEIGER, Thomas;
ALTMANN, Karl-Heinz;
FABBRO, Doriano;
DEAN, Nicholas, Mark;
MONIA, Brett;
BENNETT, Clarence, Frank
PATENT ASSIGNEE(S): NOVARTIS AG
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9732589	A1	19970912

DESIGNATED STATES
W: AL AU BA BB BG BR CA CN CU CZ EE GE HU IL IS JP KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO SG SI SK TR TT UA UZ VN YU KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.: WO 1997-EP876 A 19970224
PRIORITY INFO.: US 1996-8/612,775 19960307

L43 ANSWER 7 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1994027641 PCTFULL ED 20020513
TITLE (ENGLISH): AMPLIFICATION OF THE VITAMIN B12 UPTAKE SYSTEM USING POLYMERS
TITLE (FRENCH): AMPLIFICATION DU SYSTEME D'ADSORPTION DE LA VITAMINE B12 PAR DES POLYMERES
INVENTOR(S): RUSSELL-JONES, Gregory, John;
WESTWOOD, Steven, William;
GOULD, Alison, Ruth;
McINERNEY, Bernard, Vincent
PATENT ASSIGNEE(S): BIOTECH AUSTRALIA PTY. LIMITED;
RUSSELL-JONES, Gregory, John;
WESTWOOD, Steven, William;
GOULD, Alison, Ruth;
McINERNEY, Bernard, Vincent
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9427641	A1	19941208

DESIGNATED STATES
W: AT AU BB BG BR BY CA CH CN CZ DE DK ES FI GB GE HU JP KG KP KR KZ LK LU LV MD MG MN MW NL NO NZ PL PT RO RU SD SE SI SK TJ TT UA US UZ VN AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
APPLICATION INFO.: WO 1994-AU273 A 19940524
PRIORITY INFO.: US 1993-8/064,892 19930524

L43 ANSWER 8 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
ACCESSION NUMBER: 1991001758 PCTFULL ED 20020513
TITLE (ENGLISH): BIOLOGICALLY ACTIVE DRUG POLYMER DERIVATIVES
TITLE (FRENCH): DERIVES POLYMERES DE SUBTANCES MEDICAMENTEUSES BIOLOGIQUEMENT ACTIFS

INVENTOR(S): VERONESE, Francesco;
SARTORE, Luciana;
ORSOLINI, Piero;
DEGHENGHI, Romano
PATENT ASSIGNEE(S): DEBIOPHARM S.A.;
VERONESE, Francesco;
SARTORE, Luciana;
ORSOLINI, Piero;
DEGHENGHI, Romano
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9101758	A1	19910221

DESIGNATED STATES
W: AT BE CA CH DE DK ES FR GB IT JP LU NL SE US
APPLICATION INFO.: WO 1990-EP1261 A 19900726
PRIORITY INFO.: GB 1989-8918009.5 19890807
GB 1989-8919618.2 19890830

=> d kwic 5

L43 ANSWER 5 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN
TIEN ANTIPROLIFERATIVE COMBINATIONS, CONTAINING RAF-TARGETED OLIGONUCLEOTIDES AND CHEMOTHERAPEUTIC COMPOUNDS
ABEN The invention relates to combinations of raf-targeted (especially c-raf-targeted) deoxyribo- and ribo-oligonucleotides and derivatives thereof with other chemotherapeutic compounds, as well as to pharmaceutical preparations and/or therapies, in relation. . . activity of a regulatory protein. In particular, the invention relates to products or combinations comprising antisense oligonucleotides or oligonucleotide derivatives targeted to nucleic acids encoding raf and other (preferably standard) chemotherapeutics, either in fixed combination or for chronologically staggered or simultaneous. . . of compounds, either in fixed combination or for chronologically staggered or simultaneous administration, for the treatment of proliferative diseases, especially tumor diseases, that can be treated by inhibition of raf activity, that is, where the antisense oligonucleotides or oligonucleotide derivatives are targeted to nucleic acids encoding the regulatory protein raf or active mutated derivatives thereof.
ABFR . . . a une administration echelonnee dans le temps ou simultanee, en vue de traiter des maladies proliferatives telles que des maladies tumorales, ce traitement pouvant s'effectuer par inhibition de l'activite de raf, c'est-a-dire lorsque les oligonucleotides antisens ou leurs derives sont cibles. . .

DETD ANTIPROLIFERATIVE COMBINATIONS, CONTAINING RAF-TARGETED OLIGONUCLEOTIDES AND CHEMOTHERAPEUTIC COMPOUNDS
Field of the Invention
This invention relates to combinations of raf-targeted (especially c-raf-targeted) deoxyribo- and ribo-oligonucleotides and derivatives thereof with other chemotherapeutic compounds,

as well as to pharmaceutical preparations and/or therapies, in relation to disease. . . of the activity of a regulatory protein. In particular, the invention relates to products or combinations comprising antisense oligonucleoticles or oligonucleotide derivatives targeted to nucleic acids encoding (especially human) raf and other (preferably standard) chemotherapeutics, either in fixed combination or for chronologically staggered or simultaneous. . . both classes of compounds, either in fixed combination or for chronologically staggered or simultaneous administration, for the treatment of proliferative diseases, especially tumor diseases, that can be treated by inhibition of raf, especially c-raf, activity, that is, where the antisense oligonucleotides or oligonucleotide derivatives are targeted to nucleic acids encoding the regulatory protein raf, especially c-raf, or active mutated derivatives thereof.

. . .

decade concerning the molecular basis of mammalian cell transformation has led to the unifying concept of growth regulation and its disorders in cancer cells. The fact that many products of cancer genes encode for proteins that regulate normal mitogenesis suggests that the carcinogenic pro-cess may be viewed as a multistep and progressive. . . signal is amplified and transduced inside cells by protein kinase (PK) cascades either by receptor activated tyrosine phospho-rylation or by receptor coupling to GTP-binding proteins. Most mitogenic pathways utilize unique and/or overlapping parts of these protein kinase cascades. Accordingly mutant alleles of these PK. . . anticancer strategy is, consequently, based on the assumption that blocking deregulated mitogenic signal transduction at the level of PKs will cause cancer growth

-

inhibition. This approach is likely to identify compounds with less side effects compared to standard chemotherapeutic agents.

The raf family of serine/threonine specific protein kinases comprises three members, A-raf, B-raf and c-raf (see Magnusson et al., Sem. Cancer Biol. 5, 247-53 (1994); Beck et al., Nucl. Acids Res. 15, 595-609 (1987) and Sithanandam et al., Oncogene 5,1775-80 (1 990)). The. . . of ras protein function within the MAP kinase signaling path-way. Since ras is present in a high proportion of human cancers , novel therapies directed against raf kinases are believed to prove useful in the treatment of ras-dependent tumors.

. . .

difficulties in the raf assay. The antisense approach represents a possibility to circumvent these difficul-ties. The antisense approach allows to knock-out target genes by a highly selective and sequence-specific mechanism. The identification of antisense raf kinase inhibitors has

opened totally new approaches for the treatment of human cancer
. In addition, these drugs,
interfering with intracellular signaling, are expected to have far less
unwanted side effects
than the classical chemotherapeutic agents. . .

Summary of the invention
Surprisingly, positive and preferably even highly synergistic effects
between c-raf-targeted
oligonucleotides or oligonucleotide derivatives (ODNs) and standard
chemotherapeutic
drugs have been observed in nude mouse xenograft models. It is thus
reasonable to
assume. . . that the ODNs might be used not only as single agents,
but also especially in
combination therapy for the treatment of cancer diseases.
. . .
(up to 1 00 mg/kg have been found to be non-toxic in
animals), thus allowing great flexibility in the treatment of
cancer patients. Third, due to the
fact that the c-raf-directed ODNs open up a totally new route of
treatment, it is also possible
to treat cancer types which have been very difficult to treat
or even practically unaffected by
therapy with standard chemotherapeutics, such as small cell. . .
prostate carcinomas and also lymphomas. Fourth, in a num-
ber of cases it is even possible to bring about regression of
tumors and complete cure. Most
importantly, in none of the combination experiments antagonistic effects
are observed.
. . .
Description of the Invention
The present invention preferably relates to combination preparations
comprising a) at least
one oligonucleotide or oligonucleotide derivative (ODN) targeted
to nucleic acids encoding
raf (especially human raf)i with b) at least one other chemotherapeutic
agent; or
pharmaceutically acceptable salts of any. . .
. . .
to a method for treating a proliferative disease that can be trea-
ted by administration of an oligonucleotide or oligonucleotide
derivative targeted to raf,
eSDecially c-raf, especially where the disease responds to modulation of
raf activity, where
a) at least one oligonucleotide or oligonucleotide derivative (ODN)
targeted to nucleic acids
encoding (especially human) raf and capable of modulating (especially
human) raf
expression and
b) at least one other chemotherapeutic agent
are. . . a quantity which is jointly therapeutically
effective against proliferative diseases that can be treated by
administration of an
oligonucleotide or oligonucleofide derivative targeted to raf,
especially c-raf, or that
preferably depend on raf, especially c-raf, activity in order to treat
them, where any
component a). . .

-
The invention also relates to a product which comprises
a) at least one oligonucleotide or oligonucleotide derivative (ODN)
targeted to nucleic acids

encoding raf, especially c-raf, and
b) at least one other chemotherapeutic agent
where any component a) and/or b).can also be. . .
. .
quantity,
which is jointly effective for treating a proliferative disease that can be treated by
administration of an oligonucleotide or oligonucleotide derivative targeted to raf, especially
c-rai (preferably that can be treated by modulation of human raf, especially c-raf, activity) of
a) at least one oligonucleotide or oligonucleotide derivative (ODN) targeted to nucleic acids
encoding raf and
b) at least one other chemotherapeutic agent,
where any component a) and/or b) can also be present. . .

The invention also relates to the use of a combination of
a) at least one oligonucleotide or oligonucleotide derivative (ODN) targeted to nucleic acids
encoding raf, especially c-raf, and
b) at least one other chemotherapeutic agent,
where any component a) and/or b) can also. . . pharmaceutical preparations for use as compositions against a proliferative disease that can be treated by application of an oligonucleotide or ofigonucleotide derivative
targeted to rat, especially human c-raf, preferably a proliferative disease that can be treated
by modulation of rat (especially human c-raf) activity.

An oligonucleotide or oligonucleotide derivative (ODN) targeted to nucleic acids encoding
(especially human) rat is primarily characterized as follows: The relationship between an
such an ODN and its complementary nucleic acid target to which it hybridizes is commonly
referred to as antisense. Targeting an oligonucleotide to a chosen nuclei acid target, in
the context of this invention, is a multistep process. The process usually begins with
identifying a nucleic acid sequence of which. . . associated with a particular disease state, or for a foreign nucleic acid from an infectious agent. In the present invention, the target is a nucleic acid encoding rat, that is,
the rat gene or preferably the mRNA expressed from the rat gene. The targeting process
also includes determination of the site or sites within the nucleic acid sequence for the
oligonucleotide interaction to occur in such a way that the desired effect-modulation of
gene-expression will result. Once the target site or target sites have been identified,
oligonucleotides are selected which are sufficiently complementary to the target, i.e., that
hybridize sufficiently well and show sufficiently specific hybridization to provide the desired
modulation.

Effects on tumor growth can be measured in analogy to or in accordance with the proces-
ses taught in the examples of the present. . .
. .
are terms used to indicate a sufficient
degree of complementarity such that stable and specific binding occurs

between the DNA
and RNA target and the ODN. It is understood that an ODN need
not be 1 00 % comple-
mentary to its target nucleic acid sequence to be specifically
hybridizable. An oligonucleo-
tide is specifically hybridizable when binding of the oligonucleotide to
the target interferes
with the previously uninfluenced function of the target
molecule to cause a loss of its
effectiveness, and there is a sufficient degree of complementarity to
avoid non-specific
binding of the oligonucleotide to non-target sequences under
conditions in which specific
binding is desired, i.e. under physiological conditions in the case of
in vivo application or
therapeutic. . .

-
Preferably, an ODN is employed which is targeted to human mRNA
encoding c-raf (prefer-
ably corresponding to the sequence given in Bonner et al., Nucl.Acids
Res. 14, 1009-1015
(1 986)).. . . the 3'-untranslated region, the 5'-cap region, intron
regions and
intron/exon or splice junction ribonucleotides. Thus, oligonucleotides
may preferably be
formulated which are targeted wholly or in part to these
associated ribonucleotides. In pre-
ferred embodiments, the oligonucleotide is targeted to a
translation initiation site (AUG co-
don) or sequences in the 5'- or 3'-untranslated region of the human
c-raf mRNA.. . .

. . .
units or analogues/derivatives thereof sufficient in number
and identity to allow hybridization preferably have a length that allows
specific binding to the
target sequence, especially a length corresponding to 5 to 50
nucleotide units, preferably to
1 0 to 35 nucleotide units, more preferably. . .

. . .
from the building
blocks of a natural oligonucleotide. Thus, oligonucleotides with regard
to their backbone
may have altered sugar moieties and/or inter-sugar linkages,
and, with regard to the bases,
altered bases may be present.

With regard to the backbone, that is to the altered sugar moieties
and/or inter-sugar
linkages (internucleosidic bridges), preferred among these are
the following types.

. . .
be chimeric oligonucleotides or (ii) comprise only one type of these
units
with regard to the backbone (sugar moieties and/or inter-sugar
linkages) which is present
throughout the chain of the respective oligonucleotide derivative,
preferably oligo-2'deoxy-
nucleotide derivative, most preferably of the 2'-deoxyribose-
phosphorothioate type. At. . . preferably to one of the following
residues, but may also (in a broader
aspect of the invention) be bound to other conjugated moieties
as described below forming
conjugates. Both groups (i) and (ii) are also preferred

independently as separate group.

. . .

one or more beneficial
properties (such as, for example, increased nuclease resistance,
increased uptake into
-
cells, increased binding affinity for the RNA target,
diminished probability for sequence
independent side effects), the so-called Awin, and a region that premits
RNase H mediated
cleavage of the target complement, the so-called RNase
H-window. In one embodiment, a
chimeric oligonucleotide comprises at least one region modified to
increase target binding
affinity and, usually, a region that permits RNase H mediated cleavage
of the target com-
plement. Affinity of an oligonucleotide or an oligonucleotide derivative
for its target is rou-
tinely determined by measuring the Trn of an oligonucleotide/
target pair, which is the tempe-
rature at which the oligonucleotide or its derivative and the
target dissociate. Dissociation is
detected spectrophotometrically. The higher the Tm, the greater the
affinity of the oligonu-
cleotide for the target. Methods for Tm measurement are known
in the art (see, e.g.,
Sambrook, Fritsch and Maniatis, Molecular Cloning - A Laboratory
Manual,. . . regions M are routinely in-
corporated into oligonucleotides and these oligonucleotides have been
shown to have a
higher Tm (i.e., a higher target binding affinity) than
2'-deoxyoligonucleotides against a
given target. The effect of such increased affinity is to
greatly enhance antisense oligo-
nucleotide inhibition of raf gene expression. RNase H is. . . a
cellular endonuclease that
cleaves the RNA strand of ANA:DNA duplexes. Activation of this enzyme
therefore results
in cleavage of the RNA target, and can thus greatly enhance
the efficiency of antisense
inhibition. Cleavage of the RNA target can be routinely
demonstrated by gel electropho-
resis. In another embodiment, the chimeric oligonucleotide is also
modified to enhance
nuclease resistance. Cells. . . oligonucleotides. A
variety of oligonucleotide modifications have been demonstrated to
enhance or confer
nuclease resistance. In some cases, oligonucleotide modifications which
enhance target
binding affinity are also, independently, able to enhance nuclease
resistance. Especially
preferred is the 2'-O-CH;?CH2OCH3 (2'-(2-methoxy)ethoxy) modification or
an F at the 2'
position of at least one oligonucleotide. This modification has been
shown to increase both
the affinity for its target and nuclease resistance of the
oligonucleotide.

. . .

enhanced
uptake into cells or the oligonucleotides or oligonucleotide derivatives
in combinations ac-

cording to the invention can also be conjugated to one or more
(then identical or different)

additional moieties, for example selected from: A group forming micelles, an antibody, a carbohydrate,. . .

. . .

the term other chemotherapeutic agent there is meant any chemotherapeutic agent that is or can be used in the treatment of tumor diseases, such as chemotherapeutics derived from the following classes.

. . .

chlorambucil (Leukeran); nitrosoureas such as cyclohexylnitrosourea (meCCNU; Carmustine, BCNU, BiCNU) or lomustine (CCNU, CeeNU), cis-platinum(ll)-di-aminedichloride (platinol or cisplatin); carboplatin (Paraplatin), preferably cross-linking che-motherapeutics, preferably bis-alkylating agents, especially nitrogen mustards, such as mechlorethamine (Mustargen); alkyl sulfonates such as busulfan (Myeleran); cyclophos-pharnide; melphalan (Alkeran); chlorambucil (Leukeran); cis-platinum(il)-diaminedichloride (platinol or cisplatin) or carboplatin (Paraplatin); or compounds that form cross-links via ionic bonds, such as ethyleneirnine derivatives, e.g. triethylenethiophosphoramid (thio-tepa) (forms ionic cross-links);
(B) antitumor antibiotics, preferably selected from the group comprising bleomycine (Blenoxane); anthracyclines, such as daunomycin, dactinomycin (Cosmegen), daunorubicin (Cerubidine), doxorubicin (Adriamycin, Rubex), epirubicin, esorubicin, idarubicin (Idamycin), plicamycin (Mithracin, formerly called Mithramycin) and preferably cross-linking (bis-alkyla-ting) antitumor antibiotics, such as mitomycin C (Mitomycin, Mutamycin);
- 33 -
(C) antimetabolites, for example folic acid analogues such as methotrexate. . . (Provera, Depo-Provera); androgens such as testosterone or fluoxyrnesterone (Halotestin); estrogens such as di-ethylstilbestrol (DES), estradiol or chlorotriansiene (Tace); synthetic analogues of LHRH, such as goserelin (Zoladex); synthetic analogues of LH-releasing hormone, such as leu-prolide (Lupron, Lupron Depot); anti-androgens such as flutamide (Eulexin); anti-estrogens such. . . N-(5-benzoylamido methyl-phenyl) (3-pyridyl)-2-pyridinamin (see EP 0 564 409) or 4-(m-chloranilino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyri-midin (see EP 0 682 027);
(H) antisense oligonucleotides or oligonucleotide derivatives targeted to other targets than raf, such as those targeted to SAMDC (PCT application WO 96/05298) or protein kinase C = PKC) (international Application WO 93/19203 or WO 95/02069), especially a PKC-targeted oligonucleotide or oligonucleotide derivative (preferably of the types described as being preferred for the ODN of sequence SEQ-ID NO: 1) having. . .

More preferred is any of the above-mentioned chemotherapeutic agents except for oligo-nucleotide derivative targeted at Protein kinase C (PKC), adriamycin (doxorubicin) and

cyclophosphamide, Dreferably alone, or more preferably alone or in any combination.

-

Especially preferred are the chemotherapeutic agents mentioned above under (A) as cross-
linking chemotherapeutics, preferably bis-alkylating agents, especially nitrogen mustards, such as mechlorethamine (Mustargen); alkyl sulfonates such as busulfan (Myeleran); cyclo-phosphamide; melphalan (Alkeran); chlorambucil (Leukeran); cis-platinum(li)-diaminedichlo-ride (platinol or cisplatin) or carboplatin (Paraplatin); or compounds that form cross-links via ionic bonds, such as ethyleneimine derivatives, e.g. triethylenethiophosphoramid (thio-tepa) (forms ionic cross-links); or chemotherapeutic agents mentioned under (B) as cross-linking (bis-alkylating) antitumor antibiotics, such as mitomycin C (Mitomycin, Mutamycin).

By the term proliferative disease that can be trated by administration of an oligonucleotide or oligonucleotide derivative targeted to rafthere is preferably meant any disease that responds to such compounds; especially, by the term where the disease responds to modulation of raf activity there is preferably meant a proliferative disease selected from hyperproliferative conditions such as cancers, tumors , hyperplasias, fibrosis (especially pulmonary, but also other types of fibrosis, such as renal fibrosis), angiogenesis, psoriasis, atherosclerosis and smooth muscle cell proliferation in the blood vessels, such as stenosis or restenosis following angioplasty. Most preferably, the disease is one selected from
cancer types which have been very difficult to treat or even practically unaffected by
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therapy with standard chemotherapeutics, such as. . . .
. .
the term quantity which is jointly therapeutically effective against proliferative diseases that can be treated by an oligonucleotide or oligonucleotide derivative targeted to raf, especially c-raf, or that preferably depend on raf, especially c-raf, activity there is prefer-ably meant any quantity of the. . . of the combinations that, in the combination, is diminishing proliferation of cells responsible for any of the mentioned proliferative diseases (e.g. diminished tumor growth) or, preferably, even causing regression, more preferably even the partial or complete disappearance, of such cells (e.g. tumor regression, preferably cure). The term that depend on raf-activity is preferably intended to mean any proliferative diseases that can be influenced, especially alleviated, by hybridization of a raf-specific ODN to its target, as described hereinbefore and hereinafter.

By the term a product which comprises
a) at least one oligonucleotide or oligonucleotide derivative (ODN)

targeted to nucleic acids
encoding raf, especially human c-raf, and
b) at least one other chemotherapeutic agent
where any component a) and/or b).can also. . .
. .
although
this may also be the case). As theoretical example for mere
illustration, if a COMDonent a)
alone gives a growth of tumor cells that is diminished by a
factor of 2 in comparison to a
control without any treatment and a component b). . .
. .
which is jointly (therapeutically) effective for treating a
proliferative
disease that can be treated by administration of an oligonucleotide or
oligonucleotide
derivative targeted to (especially human) raf , especially
c-raf (preferably that can be treated
by modulation of (especially human) raf, especially c-raf, activity),.
. . proliferative diseases mentioned above, that is, which leads to
diminished proliferation
or preferably even to regression of the proliferating cells (e.g.
tumor regression) or even to
cure from the proliferative disease. This term not only comprises
combinations of any
component a) and b) where. . .

The antitumor activity of SEQ-113 NO: 1 -ODN as single agents is tested
against various hu-
man tumors transplanted subcutaneously into nude mice. The
human tumors tested are
A549 lung carcinomas (ATCC No. CCL 185), T24 bladder carcinomas (ATCC
No. HTB 4),
MDA-MB-231 breast carcinomas (ATCC HTB 26). . . and Colo 205 colon
carcinomas (ATCC
CCL 222). The ODN is given once daily by the intravenous route of
application when the
tumor reaches a mean volume of approximately 100 mm3
throughout the experiments. In a
standard experiment drug application is started at day. . . and
continued until the end of the
experiment at day 30 at doses of 6, 0.62 0.06, 0.006 mg/kg. In all
tumor types tested, the
SEQ-ID NO: I -ODN exhibits significant antitumor activity in the dose
range of 0 6.0
mg/kg. The most sensitive tumor is A549 lung carcinoma
(significant activity at 0.006
mg/kg), followed by T24 bladder and MDA-MB-231 breast carcinoma. The
SEQ-lD NO: 1. . . inactive. These results strongly indicate that the
antitumor activities of SEQ-ID
NO: 1 -ODN are the result of sequence-specific inhibition of
target gene expression in
tumors. In A549 lung carcinomas, the SEQ-ID NO: 1-ODN
downregulates c-raf mRNA levels
in a sequence-specific and time-dependent manner at a dose. . .

The effects of combinations of a component a) (raf-targeted
ODN) with a component b)
(other chemotherapeutic agent) can preferably be shown in analogy to the
methods shown
below in the passage providing examples, preferably with the animals,
tumor cell lines,
conditions and combinations mentioned there.
. . .

preferred variants of the present invention is
intended to refer to
Qi combination preparations comprising at least one oligonucleotide or
oligonucleotide
derivative (ODN) targeted to nucleic acids encoding
(especially human) raf with at least one
other chemotherapeutic agent; or
Q a method for treating a proliferative disease that can be treated by
an oligonucleotide or
oligonucleotide derivative targeted to raf, especially c-raf,
especially where the disease
responds to modulation of raf activity, where a) at least one
oligonucleotide or
oligonucleotide derivative (ODN) targeted to nucleic acids
encoding (especially human) raf
and capable of modulating (especially human) raf expression and
b) at least one other chemotherapeutic. . . combination in a quantity
which is jointly therapeutically
effective against proliferative diseases that can be treated by an
oligonucleotide or
oligonucleotide derivative targeted to raf, especially c-raf,
or that preferably depend on raf,
especially c-raf, activity in order to treat them, or
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Oil a product which comprises
a) at least one oligonucleotide or oligonucleotide derivative (ODN)
targeted to nucleic acids
encoding (especially human) raf and
b) at least one other chemotherapeutic agent
in the presence or absence of one or. . . quantity, which is jointly
effective for
treating a proliferative disease that can be treated by administration
of an oligonucleotide or
oligonucleotide derivative targeted to (especially human) raf,
especially human c-raf
(especially by modulation of human raf, especially c-raf, activity) of
a) at least one oligonucleoticle or oligonucleotide derivative (ODN)
targeted to nucleic acids
encoding (especially human) raf and
b) at least one other chemotherapeutic agent,
with one or more pharmaceutically acceptable carrier materials; or
fy) the use of a combination of
a) at least one oligonucleotide or oligonucleotide derivative (ODN)
targeted to nucleic acids
encoding (especially human) raf and
b) at least one other chemotherapeutic agent,
for producing pharmaceutical preparations for use as compositions
against a a proliferative
disease that can be treated by application of an oligonucleotide or
oligonucleoticle derivative
targeted to raf, especially human c-raf, preferably a
proliferative disease that can be treated
by modulation of raf (especially human c-raf) activity.
. . .
a combination (preferably synergistic and/or causing regression up to
and
including complete cure) of a) at least one oligonucleotide derivative
(ODN) targeted to
nucleic acids encoding human raf and preferably c-raf; the
oligonucleotide derivative
preferably being one that corresponds to an oligonucleotide derivative
as. . .
. . .
chlorambucil (Leukeran); nitrosoureas such as cyclohexylnitrosourea

(meCCNU; Carmustine, BCNU, BiCNU) or lomustine (CCNU, CeeNU), cis-platinum(li)-di-
aminedichloride (platinol or cisplatin); carboplatin (Paraplatin); preferably cross-linking che-
motherapeutics, preferably bis-aikylating agents, especially nitrogen mustards, such as
mechlorethamine (Mustargen); alkyl sulfonates such as busulfan (Myeleran); cyclophos-
phamide; melphalan (Alkeran); chlorambucil (Leukeran); cis-platinum(il)-diaminedichloride
(platinol or cisplatin) or carboplatin (Paraplatin); or compounds that form cross-links via ionic
bonds, such as ethyleneimine derivatives, e.g. triethylenethiophosphoramid (thio-tepa)
(forms ionic cross-links);
(B) antitumor antibiotics, preferably selected from the group comprising bleomycine
(Blenoxane); anthracyclines, such as daunomycin, dactinomycin (Cosmegen), daunorubicin
(Cerubidine), doxorubicin (Adriamycin, Rubex), epirubicin, esorubicin, idarubicin (Idamycin),
plicamycin (Mithracin, formerly called Mithramycin) and preferably cross-linking (bis-alkyla-
ting) antitumor antibiotics, such as mitomycin C (Mitomycin, Mutamycin);
(C) antimetabolites, for example folic acid analogues such as methotrexate (Folex, Mexate)
or. . . (Provera, Depo-Provera); androgens such as testosterone or fluoxymesterone (Halotestin);
estrogens such as di-
ethylstilbestrol (DES), estradiol or chlorotriansiene (Tace); synthetic analogues of LHRH,
such as goserelin (Zoladex); synthetic analogues of LH-releasing hormone, such as leu-
prolide (Lupron, Lupron Depot); anti-androgens such as flutamide (Eulexin); anti-estrogens
such. . . N-(S-benzoylamido methyl-phenyi) (3-pyridyl)-
2-pyridinamin (see EP 0 564 409) or 4-(m-chloranilino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyri-
midin (see EP 0 682 027);
(H) antisense oligonucleotides or oligonucleofide derivatives targeted to other targets than
raf, especially targeted to SAMDC (PCT application WO 96/05298) or (less preferably)
protein kinase C (International Application WO 93/19203 or WO 95/02069); and
- 48. . . or antibodies for active immunotherapy of melanoma (see EP 0 428 485),
more preferably
selected from the chernotherapeutics mentioned above under (A) as cross-linking
chemotherar)eutics, most preferably bis-alkylating agents, especially nitrogen mustards,
such as mechlorethamine (Mustargen); alkyl sulfonates such as busulfan (Myeleran);
cyclophosphamide; melphalan (Alkeran); chlorambucil (Leukeran); cis-platinum(li)-
diaminedichloride (platinol or cisplatin) or carboplatin (Paraplatin); compounds that form
cross-links via ionic bonds, such as ethyleneimine derivatives, e.g. triethylenethiophos-
phoramid (thio-tepa) (forms ionic cross-links); mentioned under (B) as cross-iinking (bis-
alkylating) antitumor antibiotics, such as mitomycin C (Mitomycin, Mutamycin); and

purine nucleoside analogues such as Cladribine. . .

Preferred is especially a combination of a) at least one oligonucleotide derivative (ODN)
targeted to nucleic acids encoding human c-raf and that corresponds to the following
sequence.

. . .
as of the phosphorothioate type and that have no sugar or base modification; and
and
b) at least one other chemotherapeutic agent selected from cross-linking chemotherapeutic agents, most preferably bis-alkylating agents, especially nitrogen mustards, such as mechlorethamine (Mustargen); alkyl sulfonates such as busulfan
(Myeleran); cyclophosphamide; melphalan (Alkeran); chlorambucil (Leukeran); cis-platinum(li)-diaminedichloride (platinol or cisplatin) or carboplatin (Paraplatin); from compounds
that form cross-links via ionic bonds, such as ethyleneimine derivatives, e.g. triethylene-
thiophosphoramid (thio-tepa) (forms ionic cross-links); from cross-linking (bis-alkylating)
antitumor antibiotics, such as mitomycin C (Mitomycin, Mutamycin), and from purine nucleoside analogues such as Cladribine (Leustatin; 2-chloro-2'-deoxy-P-D-adenosine), 6-mercaptopurine (Mercaptopurine,. . .

. . .
any of the embodiments of the invention defined above component b) is selected from the mentioned other chemotherapeutic
agents except for adriamycin (doxorubicin), cyclophosphamide or an oligonucleotide or
oligonucleotide derivative targeted at (especially human) PKC.

Even more preferred is a combination of a) at least one oligonucleotide derivative (ODN)
targeted to nucleic acids encoding human c-raf and that corresponds to the following
sequence.

- cisplatin for human prostate carcinomas;
- mitomycin for small lung cell carcinomas;
- cisplatin for small cell lung cancers: or
- mitomycin for large cell lung carcinomas

are in combination; where any component a) and b) can also be present in. . .

fluorouracil for colon cancer; or
mitomycin for melanoma
are in combination; where any component a) and b) can also be present in the form of a
pharmaceutically. . .

. . .
synergistic combinations given there, most specific the combinations where component
b) is not selected from adriamycin, an oligonucleotide or oligonucleotide derivative targeted
at protein kinase C and cyclophosphamide alone.

. . .
that is suitable for administration
to a warm-blooded animal, especially man, suffering from a proliferative

disease selected
from hyperproliferative conditions such as cancers,
tumors, hyperplasias, fibrosis,
angiogenesis, psoriasis, atherosclerosis and smooth muscle cell
proliferation in the blood
vessels, such as stenosis or restenosis following angioplasty. Most
preferably, the disease
is one selected from cancer types which have been very
difficult to treat or even practically
unaffected by therapy with standard chernotherapeutics, such as small
cell. . .

. . .

(Gattefoss6 S.A., Saint Priest, France), 'Gelucire
(Gattefoss6 S.A., Saint Priest, France) or sesame oil, paraffin oil or
liquid polyethylene
glycols, such as PEG 300 or 400 (Fluka, Switzerland), or
polypropylene glykols, to each of
which stabilisers or detergents may also be added, on in. . .

5'-TCC CGC CTG TGA CAT GCA TT-3'; SEQ-ID NO: 1 is a 20-mer
phosphorothioate ODN
targeting the 3'-untransiated region of c-raf mRNA which is
used in the following examples,
where it is named SEQ-ID NO: 1 -ODN.

. . .

given for 6 mice per time point, respec-
tively. Placebo treated controls receive carrier as indicated in
examples. The following hu-
man tumor cells are used for the experiments.

Estrogen receptor-positive breast cancer: MCF
Estrogen receptor-negative breast cancer: MDA-MB
Colon cancers: Colo 205, HCT 116, WiDr.

. . .

These cells were taken from the pleural effusion of a 69-year old
female Caucasian (see H.D. Soule et W., J. Nafi. Cancer Inst.
51,1409-16 (1973)). Medium
for propagation: Medium: Eagle's MEM with non-essential amino acids,
sodium pyruvate, 20
ug insulin/ml, 10 % fetal calf. . .

. . .

ATCC HTB 26. This line was isolated from the pleural effusion of a 51 -
year-old female Caucasian (see J. Natl- Cancer Inst.
(Bethesda) 53, 661-74 (1974)).

. . .

CCL 222, This cell line was isolated from ascitic fluid of a 70-year-old
Caucasian male with carcinoma of the colon (see Cancer Res.
38, 1345-55 (1978)).

. . .

cells belong to one of three strains of malignant cells
isolated in 1979 from a male patient with colon carcinoma (see
Cancer Res. 41, 1751-56
(1 981)). Medium for propagation: McCoy's 5a, 1 0 % fetal calf serum.

. . .

line was derived from the pleural fluid of a 55-year-
old Caucasian male with small cell carcinoma of the lung (see
Cancer Res. 40, 3502-7
(1 980)). Medium for propagation: RPMI 1640, 90%; fetal bovine serum, 1
0%.

. . .

(vii) NCI-H209: ATCC HTB 172. This cell line was derived from the bone
marrow of a
Caucasian male with small cell cancer of the lung (see
Cancer Res. 45, 2913-23 (1985)).

. . .
established in serum-free medium in 1982
from a lung mass taken from a male with squameous cell carcinoma of the lung (see
Cancer Res. 46, 798-806 (1986)). Medium for propagation: RPMI 1640, 90 %; fetal bovine
serum, 10%.

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(x) SK-mel 3: ATCC HTB 69. The cell line was isolated from tumor cells released by
trypsinization of lymph node metastases (see Human Tumor Cells in Vitro': pp. 1 1 5-159, J.

Natl. Cancer Inst. (Bethesda) 41, 827-31 (1968)). Medium for propagation: Eagle's Minimal
Essential Medium with non-essential amino acids, sodium pyruvate (I mM) and. . .
. . .
HTB 161. This cell line was established from the malignant ascites of a patient with progressive adenocarcinoma of the ovary (see Cancer Res. 43, 5379-89
(1 983)). Medium for propagation: RPMI with IO jAg/ml insulin, 80%; fetal bovine serum,
20%.
. . .
The cell line was initiated from a grade IV prostatic adenocarcinoma from a 62-year-old male Caucasian (see Invest. Urol. 17,16-23 (1979) and
Cancer Res, 40, 524-34 (1980)). Medium for propagation: Ham's F1 2K medium, 93 %; fetal
bovine serum, 7%.
. . .
a patient with widespread metastatic carcinoma of the prostate and a 3-year history of lymphocytic leukemia (see D.D. Mickey et al. Cancer Res. 37, 4049-4058,
(1 977)). Medium for propagation: Eagle's MEM, 1 0 % fetal calf serum.

Animals are kept under sterile conditions with free access to food and water. For all in vivo
experiments, tumors are serially passaged by a minimum of three consecutive transplanta-
tions prior to start of treatment. Tumor fragments (approx. 25 mg) are implanted s.c. into the
left flank of the animals with a 13-gauge trocar needle under Forene (Abbott, Switzerland)
anesthesia. Treatments are started when the tumors reach a mean tumor volume of ap-
proximately 1 00 mm3. Tumor growth is monitored twice weekly and 24 hours after the last
treatment by measuring perpendicular diameters. Tumor volumes are calculated as descri-
- 74 -
bed (Evans, BID, Mith, IE, Shorthouse, AJ, Millar, JJ. A comparison of the response of hu-
man cell carcinoma to vindesine and vincristine. Brit. J. Cancer 45, 466-468 (1982)). T/C %
data are percent values of Tumor versus Control.

Ex. 1 placebo and SEQ-ID NO: 1 -ODN: once daily for 32 consecutive days starting with day 6 after tumor transplantation; adriamycin: once weekly on
days 6 and 13; ifosfamide: once weekly for 4 consecutive weeks (on days 69 13, 20 and. . .

Ex. 2 placebo: once daily for 21 consecutive days, starting with day 7 after tumor
transplantation; SEQ-ID NO: 1 -ODN: once daily for 29 consecutive days, starting with day 7 after tumor transplantation; adriamycin: once weekly on
day 7, 14 and 28, respectively.

Ex. 3 placebo: twice daily for 21 days, starting with day 12 after tumor
transplantation; SEQ-ID NO: 1 -ODN and estracyt: once daily for 21 consecutive days, starting with day 12 after tumor
transplantation; cisplatin.

once a week on days 12 and 19 after tumor transplantation.
. . .
consecutive days,
starting on day 4 after transplantation; adriamycin, cisplatin and 5-fluoro
uracil: once weekly on days 4 and 1 1 after tumor
transplantation.
. . .
14 consecutive days, starting on day 4 after transplan
tation; mitomycin: once weekly on days 4, 1 1 and 18 after tumor transplan
tation; ifosfamide: once weekly on days 49 11 and 18 after transplantation;
cisplatin: once weekly on days 4 and 1 1. . .
. . .
9 1 8 and 25 after transplantation;
adriamycin and mitomycin: once weekly on day 1 1 9 18 and 25 after tumor
transplantation; SEQ-ID NO: 1 -ODN: once daily starting on day 1 1 after transplantation.

Treatment Tumor volume in MM3 (mean sem) on itq2i
day day day day day day day
6 9 13 20 27 31 38
Placebo treated. . .

Treatment Tumor volume in mm' (mean ± sem) on TIC
day day day day day day day
7 11 15 18 22 25 28
Placebo. . . NO ODN in combination with estracz or cisplatin against the s.c. transplanted human prostate carcinoma PC3 in male Balb/c nude mice
Treatment Tumor volume in MM3 (mean ± sem) on RQ!i
day day day day day
12 19 22 26 33
Placebo treated controls 113 281. . . NO-1 -ODN in combination with estracId or cisplatin a-gains
the s.c. transplanted human prostate carcinoma DU145 in male Balb/c nude mice
Treatment Tumor volume in MM3 (mean ± sem) on IIQ!i
day day day day day
9 13 17 20 23
Placebo treated controls 116 451. . . -ODN in combination with 5-fluorouracil or adriamycin
against the s.c. transplanted human colon carcinoma Colo 205 in female Balb/6 nude mice
Treatment Tumor volume in MM3 (mean sern) on It0i
day day day day day
12 17 20 24 29
Placebo treated controls 116 253 515. . .

Treatment Tumor volume in MM3 (mean sem) on itq2i
day day day day day
4 7 1 1 1 4 1 9
Placebo treated controls. . .

Treatment Tumor volume in MM3 (mean sem) on T/CO/O
day day day day day
10 17 24 28 35
Placebo treated controls 126 306 857. . .

Treatment Tumor volume in MM3 (mean sern) on R92i
day day day day day day (day
13 21 25 30 35 41 35)
Placebo treated. . .

Treatment Tumor volume in mm3 (mean ± sem) on
day day day day day day (day
4 8 1 1 1 4 1 8. . .

Treatment Tumor volume in MM3 (mean sem) on
day day day day
8 12 16 20
Placebo treated controls 187 529 980 1739 100
(NaCl 0.9%,. . .

Treatment Tumor volume in rnm3 (mean ± sem) on Uc]]
day day day day day
1 4 1 8 21 25 29
Placebo treated controls. . .

Treatment Tumor volume in MM3 (mean sem) on TLC-010
day day day day
11 18 25 32
Placebo treated controls 126 269 635 1025 100
(NaCI. . .

Treatment Tumor volume in MM3 (mean ± sem) on 1192i
day day day day day day
6 13 20 27 34 41
Placebo treated controls. . . chemotherapeutic drugs adriamycin, estracyt, cisplatin, 5-fluorouracil, mitomycin, ifosfamide and tamoxifen are applied according to established chemotherapeutic schedules
- 90 -
for the respective tumor types. The SEQ-ID NO: 1 -ODN exerts improved antitumor effects with adriamycin, estracyt, 5-fluorouracil, ifosfamide and tamoxifen against human breast, prostate, colon, ovarian and melanoma tumors transplanted into nude mice. The combinations of SEQ-ID NO: 1 -ODN with fluorouracil in human Colo2O5 colon carcinomas results in strong tumor regression. The combinations of SEQ-ID NO: 1 -ODN with mitomycin in SK-mel3 melanomas results in strong regression in all and. . . of SEQ-lD NO: 1 -ODN with cisplatin in PC3 human prostate carcinomas result in an especially highly synergistic effect with complete tumor cures observed. The combination of SEQ-lD NO: 1-ODN and mitomycin in NCI-H69 lung carcinomas also results in a strong synergistic antitumor effect. . . complete cures. The same result is found with the combination of SEQ-ID NO: I -ODN and

cisplatin in NCI-H69
small cell lung cancers and with the combination of SEQ-1D NO:
1 -ODN and mitomycin in
NCI-H460 large cell carcinomas. In other lung carcinomas, positive. . .
beneficial
antitumor effects both as single agent and in an improved manner in
combination with
chemotherapeutic drugs in the treatment of human cancer.

CLMEN 1 A method for treating a proliferative disease that can be treated by
administration of an
oligonucleotide or oligonucleotide derivative targeted to raf,
where a) at least one
oligonucleotide or oligonucleotide derivative targeted to
nucleic acids encoding raf and
capable of modulating raf expression and
b) at least one other chemotherapeutic agent
are administered to a. . . a quantity which is jointly
therapeutically
effective against proliferative diseases that can be treated by
administration of an
oligonucleotide or oligonucleotide derivative targeted to raf
in order to treat them, where any
component a) and/or b) can also be present in the form of. . .

3 The method according to claim 1 wherein the combination of component
a) and b) leads
to synergism or to tumor regression, or both.

. . .
cyclophospharnide; 4-hydroxyperoxycyclophos'phamide;
rnafosfamide; ifosfamide; melphalan; chlorambucil; nitrosoureas;
cis-plafinum(11)-di-
aminedichloride; and carboplatin;
- 94 -
(B) antitumor antibiotics selected from the group comprising bleomycine;
anthracyclines;
and cross-linking antitumor antibiotics;
(C) antimetabolites selected from the group comprising folic acid
analogues; purine
nucleoside analogues; pyrimidine analogues; hydroxyurea; and polyamine
biosynthesis
inhibitors;
(D) plant. . . selected from the group comprising vinca alkaloids;
and
epipodophyllotoxins;
(E) hormonal agents and antagonists selected from adrenocorticoids;
progestines;
androgens; estrogens; synthetic analogues of LHRH; synthetic
analogues of LH-releasing
hormone; anti-androgens; anti-estrogens; aromatase inhibitors; adrenal
cyctooxic agents;
somatostatine analogues; and 5a-reductase inhibitors;
(F) biological response modifiers selected from lymphokines; and
interferons;
(G) inhibitors of protein tyrosine kinases and/or serine/threonine
kinases other than ODNs;
(H) antisense oligonucleotides or oligonucleotide derivatives
targeted to other targets than
raf; and
(1) miscellaneous agents or agents with other or unknown mechanism of
action selected
from S-triazine derivatives; enzymes; methylhydrazine derivatives;
matrix. . .
. . .

methyl-phenyll (3-pyridyl) pyrimidine, N-
(3-chlorophenyl) (2-(3-hydroxy)-propyl-amino pyridyl) pyrimidinamin,
N-benzoyl-stau-
rosporine, 4,5-bis(anilino)-phthalimide, N-(5-benzoylamido
methyl-phenyl) (3-pyridyl)
pyridinamin and 4-(m-chloranilino)-5,6-dimethyl-7H-pyrrolo[2,3-
d]pyrimidin;
(H) antisense oligonucleotides or oligonucleotide derivatives
targeted to other targets
selected from SAMDC and protein kinase C; and
(1) miscellaneous agents or agents with other or unknown mechanism of
action selected
from altrematine;. . .
. . .
least one other chemotherapeutic agent selected from
bis-alkylating agents selected from the group comprising
mechlorethamine, busulfan,
melphalan, chlorambucil, cis-platinum(li)-diaminedichloride, carboplatin
and triethylene-
thiophosphoramid; cross-linking antitumor antibiotics selected
from mitornycin C; and purine
nucleoside analogues selected from Cladribine, 6-mercaptopurine,
pentostatin and 6-
thioguanine; and pyrimidine analogues selected. . .

9 The method according to claim 1 wherein the disease to be treated is
selected from
cancers, tumors, hyperplasias, fibrosis,
angiogenesis, psoriasis, atherosclerosis and smooth
muscle cell proliferation in the blood vessels.
1 0. The method according to claim 1. . .
. . .
of the
respective proliferative disease:
- cisplatin for human prostate carcinomas;
- mitomycin for small lung cell carcinomas;
- cisplatin for small cell lung cancers: or
- mitomycin for large cell lung carcinomas
are in combination; where any component a) and b) can also be present
in. . .
. . .
analogue, and
b) any one of the following other chemotherapeutic agents for the
treament of the
respective proliferative disease:
- fluorouracil for colon cancer; or
- mitomycin for melanoma
are in combination; where any component a) and b) can also be present in
the form of. . .
. . .
quantity, which is jointly effective for
treating a proliferative disease that can be treated by administration
of an oligonucleotide or
oligonucleotide derivative targeted to raf, of
a) at least one oligonucleotide or oligonucleotide derivative (ODN)
targeted to nucleic acids
encoding raf and
b) at least one other chemotherapeutic agent,
- 103 -
where any component a) and/or b) can also. . .
. . .
16 A pharmaceutical preparation according to claim 14 wherein the
combination of
component a) and b) leads to synergism or to tumor regression,

or both.

. . .

alkyl sulfonates; cyclophosphamide; 4-hydroxyperoxycyclophosphamide; mafosfamide; ifosfarnide; melphalan; chlorambucil; nitrosoureas; cis-platinum(ll)-di-
arninedichloride; and carboplatin;
(B) antitumor antibiotics selected from the group comprising bleomycine; anthracyclines;
and cross-linking antitumor antibiotics;
(C) antimetabolites selected from the group comprising folic acid analogues; purine
nucleoside analogues; pyrimidine analogues; hydroxyurea; and polyarnine biosynthesis
inhibitors;
(D) plant. . . selected from the group comprising vinca alkaloids; and
epipodophyllotoxins;
(E) hormonal agents and antagonists selected from adrenocorticoids; progestines;
androgens; estrogens; synthetic analogues of LHRH; synthetic analogues of LH-releasing
- 104 -
hormone; anti-androgens; anti-estrogens; aromatase inhibitors; adrenal cyctooxic agents;
somatostatine analogues; and 5a-reductase inhibitors;
(F) biological response modifiers. . . from lymphokines; and interferons;
(G) inhibitors of protein tyrosine kinases and/or serine/threonine kinases other than ODNs;
(H) antisense oligonucleotides or oligonucleotide derivatives targeted to other targets than
raf; and
(1) miscellaneous agents or agents with other or unknown mechanism of action selected
from S-triazine derivatives; enzymes; methylhydrazine derivatives; matrix. . . methyl-phenyll (3-pyridyl)]pyrimidine, N-
(3-chlorophenyl) (2-(3-hydroxy)-propyl-amino pyridyl) pyrimidinamin, N-benzoyl-stau-
rosporine, 4,5-bis(anilino)-phthalimide, N-(5-benzoylamido methyl-phenyl) (3-pyridyl)
pyridinamin and 4-(m-chloranilino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidin;
(H) antisense oligonucleotides or oligonucleotide derivatives targeted to other targets
selected from SAMDC and protein kinase C; and
(1) miscellaneous agents or agents with other or unknown mechanism of-action selected
from altrematine; asparaginase;. . .

. . .

least one other chemotherapeutic agent selected from
bis-alkyiating agents selected from the group comprising mechlorethamine, busulfan,
melphalan, chlorambucil, cis-platinum(li)-diaminedichloride, carboplatin and triethylene-
thiophosphoramid; cross-linking antitumor antibiotics selected from mitomycin C; and purine
nucleoside analogues selected from Cladribine, 6-mercaptopurine, pentostatin and 6-
thioguanine; and pyrimidine analogues selected. . . one salt-forming group is present.

. A pharmaceutical preparation according to claim 14 wherein the disease to be treated is
selected from cancers, tumors, hyperplasias,
fibrosis, angiogenesis, psoriasis,

atherosclerosis and smooth muscle cell proliferation in the blood vessels.

. . .

of the
respective proliferative disease:
- cisplatin for human prostate carcinomas;
- mitornycin for small lung cell carcinomas;
- cisplatin for small cell lung cancers: or
- mitomycin for large cell lung carcinomas
are in combination; where any component a) and b) can also be present in. . .

. . .

analogue, and
b) any one of the following other chemotherapeutic agents for the trearnent of the
respective proliferative disease:
- fluorouracil for colon cancer; or
- mitomycin for melanoma
are in combination; where any component a) and b) can also be present in the form of. . .

29 A combination preparation comprising a) at least one oligonucleotide or oligonucleotide
derivative targeted to nucleic acids encoding raf with b) at least one other chemotherapeutic
agent; or pharmaceutically acceptable salts of any component a),. . .

30 A product which comprises
a) at least one oligonucleotide or oligonucleotide derivative (ODN) targeted to nucleic acids
encoding raf and
b) at least one other chemotherapeutic agent
where any component a) and/or b).can also be present in. . .

31 The use of a combination of
a) at least one oligonucleotide or oligonucleotide derivative (ODN) targeted to nucleic acids
encoding raf and
b) at least one other chemotherapeutic agent,
where any component a) and/or b) can also be present. . .
pharmaceutical preparations for use as compositions against a proliferative
disease that can be treated by application of an oligonucleotide or oligonucleotide derivative
targeted to raf.

=> d kwic 8

L43 ANSWER 8 OF 8 PCTFULL COPYRIGHT 2006 Univentio on STN

DETD . . . polymer-protein bond by specific enzymes
in the body; difficulty of introduction into the polymer-drugs adduct amino acid sequences which may confer targeting properties to the adducts itself. These disadvantages are related to the chemistry employed in the polymer activation
- linkage to the drua.

. . .

drug, selected from the following species
enzymes such as superox-idedismutase, ribonuclease, arginase, asparaginase, urokinase, e.g.;
NVO 91/01758 PCF/EP90/01261
3
ant4biot4 CS such as ampic 4n, doxorubicin e. C.

peptides such as LHRH and svnthet.-c ana,ogues of same, somatostatin and synthetic analogues of same, e.g.; proteins such as interleukin-2, tumor necrosis factor, insulin, IGF-1 e.g.; nucleosides such as adenin-arabinoside (ara-A), cytosin-arabinoside (ara-C), acyclovir e.g.

The method of the invention is based on the linkaae of an amino acid or peptide spacer arm of various structures and properties to the hydroxyl function of monoalkoxy-polyethylene glycol through a carbonate linkage which involves the NH2 group of the amino acid or peptide. This reaction is followed by the activation of the COOH function of. . .

By means of the introduction of such a new spacer arm (amino acid or peptide) an improved targeting of the bioactive protein or drug is achieved : an enhanced lyposomal degradation of the peptide derivative of formula (I), a site-specific cleavage. . .

Some of these interesting properties are illustrated in the following Examples which are not limitative. in the said Examples the term I'M-PEG defines a monomethoxv-polyethylene glycol and the amino acids or peptides are described by means of the terms usual in the art.

A. Preparation of activated M-PEG with an amino acid or peptide spacer arm.

Exa=le 1
M-PEG 5000-Gly-Succinimidyl ester (M-PEG 5000-Gly-OSu)
To 10 g (2mM) of M-PEG-5000, dissolved in 50 ml of anhydrous methylene chloride, 0.56 ml (4mM) of triethylamine (TEA) and 0.81 g (4 mM) of 4-nitrophenyl chloroformate. . .

PEG-p-nitrophe-nylcarbonate (M-PEG-OCO-OPh.-NO-/), spect-rophotometrically on the basIS of p-n.-]'ropheno-' absorption was over 95%.

water, the solution was adjusted to pH 8 8.3 and added under stirring of 10.33 g (2 mM) of M-PEG-OC0 Ph-N02 while the pH was maintained at 8.3 with NaOH. After 4 hrs at room tem-oerature the solution, cooled at OOC and. . .

M-PEG-Gly-OH 10.2 g (2mM) was dissolved in 50 ml of anhydrous methylene chloride, cooled to OOC,, and 0.46 g (4 mM) of N-hydroxysuccinimide. . .

Starting from M-PEG 1900 the M-PEG Gly-OSu derivative was obtained following the same procedure with a similar yield.,
Example 2
M-PEG 5000-Trip-succinimidyl ester (M-PEG 5000-Tr-o-OS1.2)
The procedure described above gave the PEG-tryptophan derivative with a yield of 80% calculated on the

basis of the hvdroxvsuccinimide abscrDtion as weLL as tlne tryptophan absorption. . .

Examiple 3

M-PEG Phe-si.2cginimidyl ester (M-PEG 5000-Phe-OSu)
Following the procedure reported in Example 1 the M-PEG phenylalanine derivative was obtained. The produc= gave the siDectra reDorted in Figure 2 with the typical phenylalanine ab-psor-ption at 260 nm (F4a.. . .

Examr)le 4
M-PEG-nor-Le]i-succinimidyl ester (M-PEG nor-Leu-OSu)
This derivative was obtained as above described with both M-PEG 5000 and M-PEG 1900. The 95% yield was calculated
by nor-Leu evaluation on an amino acid analyzer after acid hydrolysis.

Exam-ple
M-PEG 5000-Gly-Giv-succinimidyl ester (M-PEG -Gly-Giv-
Osu)
Using Gly-Gly as a model compound, the procedure already described under Example 1 was followed to prepare an activated monomethoxy polyethylene glycol. . .

B. Bioactive substances modification with amino acid derivatized M-PEG.

Exam-Cie 6
Superoxide dismutase modifica-!:L=
With M-PEG 5000-Gly-OSu.
. . .
(SOD, EC 1 1) (100
mg) were dissolved in 10 ml of borate buffer 0.2M DH 8 and 640 mg of M-PEG 5000-Gly-OSu were added at room temperature under vigorous stirring while the pH was maintained. The mixture was left standing for 30 min.

The extent of linked polymer chains, determined on the basis of amino groups modification evaluated according to the method of trinitrophenylation of Snyder and Sabocinsk., (Snyder S.I.. . .
. . .
twice ultrafil-
tration on a PM 10 AMICON membrane and the concentrated enzyme chromatographied on a BIO-GEL A 0.5 m column. The M-PEG modified enzyme is eluted -first as symetrical peak as revealed by UV absorption (Fig. 3a), iodine reaction for M-PEG and enzymatic activity. The excess of M-PEG is eluted
later followed by the leaving group hydroxysucc.4nimide. The protein peak fractions are collected and lyophylized after membrane ultrafiltration. The M-PEG modified SOD is stored at OOC in a dessicator.

6,2 - With M-PEG Trp-OSu
The reaction was carried out as reported above (see 6.1); a similar extent of linked polymer chains to SOD and enzyme activity reduction was observed while the product presented the spectrum reported in Fig. 3 where the contribution. . .

6.3 - With M-PEG 5000-nor-Leu-OSu
The reaction carried out as reported in 6.1 gave a product with similar enzymatic properties and extent of modification bv TNBS assay. In this case the amino acid

analysis after acid hydrolysis revealed the presence of norleucine which accounted for 18 M-PEG chains bound to each SOD molecule in agreement with the TNBS test.

6.4 - With M-PEG 1900-Gly-OSu
The reaction was carried out as in 6 , s]]4'lar results were obtained as far as polymer 'linkage and enzymatic activity is concerned, thi's product is eluted later from the column as exDected from the lower molecular weight of the polymer. . .

Comment to examples 6.1 through 6.4: the puri-fication from unreacted M-PEG 5000 or M-PEG 1900 could be
succesfully reached by dilution of the reaction mixture (about 1 to 10 folds) followed by ultrafilt-ration concentration on an AMICON. . .

Pharmacokinetic behavior of native and M-PEG-modified SOD
Unmodified yeast superoxide dismutase (5.5 mg) or equiactive amount of SOD modified with M-PEG 5000-Gly or M-PEG 1900-Gly were injected into the tail vein of Wistar albine male rats.

Enzymatic properties
The stability of the M-PEG 1900 and M-PEG 500C modified yeast superoxide dismutase to different conditions are as follows
a. The M-PEG modified enzyme is less stable to incubation in a protein denaturan-z] suc.] 21M guanidinium chloride; after 4 hrs its residual activity is 10. . .

b. The M-PEG 5000-Gly-SOD was maintained in water at a concentration of 1 mgml at o', 20' or 35'C. No loss of activity was found. . .

The M-PEG 5000-Gly-SOD was found to be stable to repeated freezing and thawing cycles.

I
A M-PEG enzyme solution was evaporated to dryness at low temperature under vacuum, dissolved and again concentrated; the M-PEG modified enzyme was stable for at least six of such cycles while the unmodif-Led .enzyme lost at least 15 % of its. . .

The M-PEG 5000-Gly-SOD was completely stable to repeated cycles of dissolution and lyophilization whereas the free enzyme at each treatment lost about 5% of-its activity.

The M-PEG 5000-Gly-SOD, in 'the presence cf me-, chelates, was found to lose with greater d' the metals essential for the activity as compared. . .

Exam)ie
Arginase modification (M-PEG 5000-Giv-arciinase
Bovine liver arginase (ECI 3 3.1), 100 mg, Inlighly aCt4 V]
Durified according to 1.1terature to give a specific of 1900 IU/mg, was dissolved in 1.5 ml of carbonate bufffer pH 8.5f 0.2 M and 800 mg of M-PEG 5000-Glv-OSu were added under

vigorous stirring while the pH was maintained by a pH-stat with NaOH 0. 1 N in a microburette.. . . with water and ultrafilitered
at 4C with an AMICON PM 10 ultrafiltration membrane to reduce the volume to about 5 ml. The M-PEG modified arainase was purified from excess reagent and by-products of reaction through column chromatography as reported in Example 1. The binding of polymer. . .

Enzymatic and pharmacokinetic properties of M-PEG Giv-arainase
The modification increased the stability of the enzyme to the action of proteolyctic enzymes such trypsin, chimotrypsin, elastase and subtilysin.

The pharmacokinetic behavior of native and PEG derivatized enzyme was evaluated in tht_ rats as reportea under example 6 A 50% clearance time of 1.5 and 8 hrs was respectively. . .

Ex mL]Ie 8
Ribonuclease modification (M-PEG SON-Glv-ribon]:ciease)
Ribonuclease A (EC 2 7.16) from bovine pancreas was modified and purified as in example 6 The amount of M-PEG-Gly-OSu used for the modification was at a molar ratio of 2.5:1 calculated on the available amino groups of the enzymes. The modification resulted in the covalent linkage of 11 molecules of polymer for ribonuclease molecule.

Examyle a
Urokinase modification (M-PEG Gly-iarokinase)
Urokinase (EC 3 4.a) from urine was mod.,fied and purified as reported under example 6 With this enzyme the modification was carried out using a molar ratio of activated polymer/protein amino group of 1:2. Under these circumstances about 10 molecules of Dolymer were linked to each urokinase molecule. The enzymatic activity evaluated on the lysis of thrombus was 30% of that of the native enzyme while its. . .

Exam-Ole 10
Am-picillin modification
10.1 M-PEG 5000-Gly-Ampicillin
To a solution of ampicillin sodium salt, 50 mg (0,135 mM) in 5 ml of borate buffer 0,2 M pH 81 600 mg (0,12 mM) of M-PEG 5000-Gly-OSu were added under vigorous stirring.
. .
off ampicillin and of side products of reaction by gel filtration chromatography on a BIO GEL P 60 100-200 mesh column. The M-PEG modified drua was eluted first as a symmetric peak as revealed the UV absorption of amDicillin and the iodine reaction for PEG.

10.2 - M-PEG 5000-Gly-Ampicillin
AmiDicillin sodium salt 100 mg (0.27 mM) were solved in 20 ml of N. N-dimethylf ormamide (DMF) ; 1. 0 g (0. 2 nuM) o ff M-PEG 5000-Glv-OSu and 0.03 ml of 4-methvlmorDhol-ine (NMM) were added while pH was adjusted at 8 3 with NMM. The reaction mixture was. . .

ExamT)le 11
Doxorubicin modification (M-PEG 5000-Gly-doxorubicin)
To a solution of doxorubicin hydrocloride, 50 mg

(8 10-2 mM) of M-PEG 5000-Gly-OSu were added in portions.
. . .
free drug and the
leaving group hydroxysuccinimid by gel filtration
chromatography on a BIO GEL P 60 100-200 mesh column. The M-
- 14
PEG modified drug was eluted as a peak W4]1]
the -'ypica. UV
absorption of -doxorubicine (OD 230 and 480 nm'/ and the
expected iodine reaction -for MPEG. The M-PEG 5000-SI-v-
doxorubicin fractions were collected, concen-]rated by
ultrafiltration and lyophilized. The product was further
purified by chromatography on a BIO GEL A 0.5 m. . .

CLMEN. . . with the adjacent NH group represents the
residue of a biologically active peptide, protein or
drug selected from superoxidedismutase, ribonuclease,
arginase, asparaginase, urokinase, ampicilline,doxoru-
bicine, N-desmethyl-tamixofen, LHRH and synthetic ana-
logues of same, somatostatin and synthetic analogues of
same, calcitonin, interleukin-2, tumor necrosis factor,
insulin, IGF-1, natural or recombinant interferon, ade-
nin-arabinoside (ara-A), cytosin-arabinoside (ara-C) or
acyclovir.
-
Method for n-]eparina biologically active dr,.,a pc-
lymer derivatives 'Diaving. . . combined with the adjacent NH group
repre-
sents a biologically active peptide, protein or
drug residue selected from superoxidedismutase,
ribonuclease, arginase, asparaginase, urokinase,
ampicilline, doxorubicine, N-desmethyl-tamoxilfen,
LHRH and synthetic analogues of same, somatostatin
and synthetic analogues of same, calcit-onin, in-
terleukin-2, tumor necrosis factor, insulin, IG.F-1
natural or recombinant interferon, adenin-arabino-
side (ara-A), cytosin-arabinoside (ara-C) or acy-
clovir.
. . .
6 Pharmaceutical composition according to claim 5
which comprises as active ingredient a biologically active
drug polymer derivative selected from the group consisting
of
M-PEG 5000-Gly-superoxidedismutase,
M-PEG 5000-Trp-superoxidedismutase,
M-PEG 5000-nor-Leu-superoxidedismutase
M-PEG 1900-Gly-superoxidedismutase,
M-PEG 5000-Gly-arginase,
M-PEG 5000-Gly-.ribonuclease,
M-PEG 5000-Gly-urokinase,
M-PEG 5000-Gly-ampicill.in, and
M-PEG 5000-Gly-doxorubicin
wherein M-PEG represents monomethoxy-polve-.hvlene.

=> d his

(FILE 'HOME' ENTERED AT 11:38:17 ON 10 OCT 2006)

FILE 'MEDLINE' ENTERED AT 11:38:30 ON 10 OCT 2006
L1 10594 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
L2 1850590 S CANCER? OR NEOPLAS? OR TUMOR?
L3 2438 S L2 AND L1
L4 787167 S TARGET? OR TRANSPORT? OR HOMING OR HOME

```
L5          321 S L4 AND L3
L6       658920 S CONJUGAT? OR LINK? OR COUPL?
L7           92 S L6 AND L5
L8            2 S L7 AND (PEG OR (POLY () ETHYLENE GLYCOL))
L9           46 S L7 NOT PY>2002
L10          37 S L7 NOT PY>2001

     FILE 'CAPLUS' ENTERED AT 11:44:31 ON 10 OCT 2006
L11       18828 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
L12      735161 S CANCER? OR NEOPLAS? OR TUMOR?
L13     1280700 S TARGET? OR TRANSPORT? OR HOMING OR HOME
L14     1422867 S CONJUGAT? OR LINK? OR COUPL?
L15           6 S L7 AND (PEG OR (POLY () ETHYLENE GLYCOL))
L16       47211 S (PEG OR (POLY () ETHYLENE GLYCOL))
L17          47 S L16 AND L11
L18          19 S L17 AND L12
L19           7 S L18 AND L13
L20           0 S L19 NOT PY>2002
L21           1 S L19 NOT PY>2003
L22       15450 S DOXORUBICIN
L23         256 S L22 (L) L16
L24         118 S L23 AND L13
L25           0 S L24 AND L11
L26          52 S L24 NOT PY>2001

     FILE 'PCTFULL' ENTERED AT 11:49:06 ON 10 OCT 2006
L27        6069 S BH3 OR (LHRH OR LUTEINIZING HORMONE () RELEASING HORMONE)
L28      102117 S CANCER? OR NEOPLAS? OR TUMOR?
L29      382854 S TARGET? OR TRANSPORT? OR HOMING OR HOME
L30      530007 S CONJUGAT? OR LINK? OR COUPL?
L31       44564 S (PEG OR (POLY () ETHYLENE GLYCOL))
L32        4089 S L27 AND L28
L33        3135 S L32 AND L29
L34        3135 S L33 AND L3
L35        2910 S L33 AND L30
L36         907 S L35 AND L31
L37          27 S L36 AND DOX
L38         454 S L36 AND DOX?
L39          95 S L38 NOT PY>2001
L40         121 S L27/AB
L41         762 S L27/CLM
L42         789 S L41 OR L40
L43           8 S L42 AND L39

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L43    ANSWER 3 OF 8      PCTFULL   COPYRIGHT 2006 Univentio on STN
TIEN   COMPOSITIONS AND METHODS FOR THE PREVENTION OR TREATMENT OF
       CANCER AND BONE LOSS ASSOCIATED WITH CANCER
TIFR   COMPOSITIONS ET PROCEDES PERMETTANT LA PREVENTION OU LE TRAITEMENT DU
       CANCER ET DE LA PERTE OSSEUSE ASSOCIEE AU CANCER
ABEN   The present invention relates to compositions and methods for the
       prevention and/or treatment of bone loss associated with cancer
       . More particularly, the invention relates to OPG compositions and
       methods for the prevention and/or treatment of bone loss comprising
       said.  .  .

DETD   COMPOSITIONS AND METHODS FOR THE PREVENTION OR
       TREATMENT OF CANCER AND BONE LOSS ASSOCIATED WITH
         CANCER
       Field of the Invention
       The present invention relates to compositions
       and methods for the prevention and/or treatment of bone
       loss associated with cancer. more particularly, the
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invention relates to compositions comprising OPG and methods for the prevention and/or treatment of bone loss comprising said compositions. The. . .

Backcrround of the Invention

Many cancers can become established in tissues and organs which are far removed from the original site of tumor growth. Such cancers, termed metastatic cancers, can cause widespread complications that are often fatal. The skeleton is a common site for the spread of solid tumors, exceeded in frequency by only the liver and the lung. As a result of invasion by cancer cells, osteoclasts, the primary cells in bone that promote bone resorption, become hyperactivated and begin to break down bone at an accelerated rate.. . . such as parathyroid hormone-related peptide (PTHrP) and interleukin-1 (IL-1), both of which are increased in the bone microenvironment and are also produced by tumor cells. Patients with bone cancer frequently develop lytic bone lesions as a result of increased osteoclast activity. This condition is referred to as osteolytic bone metastasis. Bone lysis can. . . to pathologic fractures, spinal collapse, hypercalcemic events and bone pain and is a major cause of mortality and morbidity. Alternatively, as in prostate cancer bone metastases, increased osteoclastic bone destruction is accompanied by increased but disorganized bone formation (Kylmaelae et al. Brit. J.

Cancer 71, 1061-1064 (1995)). The original bone is removed, and replaced by woven unstructured bone so that the architectural integrity of the bone. . .

In addition osteoclast activity may increase the propensity of cancer cells to metastasize to bone and then to grow in that environment. Osteoclasts have been shown to release cytokines such as IL-6 which is a growth factor for some hematologic tumor cells such as multiple myeloma cells (0Keefe et al. Lab. Invest. 76, 457-465 (1997)). In addition, osteoclasts have been shown to release growth. . . matrix during bone resorption. These include fibroblast growth factors and transforming growth factor 0 which are known to promote growth of many solid tumors. In this way osteoclastic activity could create a fertile environment for metastatic seeding within bone, and as the tumor cells begin to grow and promote bone resorption, cause release of growth factors from the bone to sustain tumor expansion.

Currently available cancer therapy agents can reduce or inhibit tumor growth but have little effect on underlying lytic bone disease. It has been reported that some chemotherapeutic regimens actually contribute to bone loss. . . with hematological. malignancies such as multiple myeloma and Hodgkin's disease and in the case of gonadotrophin releasing hormone receptor agonists. In addition, once cancer has spread to the bone, it becomes more difficult to treat using current regimens. It is therefore desirable to be able to prevent. . .

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reduce the rate at which bone is broken down. Such agents may be

useful in preventing and/or treating bone resorption associated with bone cancer. It has been reported that bisphosphonates such as risedronate, ibandronate and pamidronate, which are anti-resorptive compounds, can reduce the severity of skeletal events (e.g., pathological fractures, spinal collapse, radiation of or surgery on bone) in mouse tumor models and in patients suffering from breast cancer and multiple myeloma and other tumor bone metastases. In addition bisphosphonates have been reported to reduce bone pain and other skeletal events in prostate cancer bone metastases. However, bisphosphonates have been shown to have limited efficacy with only a modest reduction in skeletal events even when given in. . .

Consequently, it is an object of the invention to provide alternative methods and compositions for the treatment of bone loss associated with cancer that overcome many of the problems associated with current therapy.

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It is a further object of the invention to provide alternative methods and compositions for the prevention of bone loss associated with cancer by prophylactic treatment to decrease the incidence of bone metastasis and/or to delay the onset of bone metastasis.

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a mammal comprising administering a therapeutically effective amount of an OPG polypeptide. Lytic bone disease is commonly observed in a mammal suffering from cancer which has metastasized to bone. Examples of such cancers include breast, prostate, thyroid, kidney, lung, esophageal, rectal, bladder, and cervical cancers as well as cancer of the gastrointestinal tract. Also included are certain hematological malignancies, such as multiple myeloma, leukemia and lymphomas, such as Hodgkin's Disease. Also included. . . mixed lytic and osteosclerotic metastases which are associated with bone pain and the loss of the structural integrity of bone as in tumors such as prostate cancer.

The invention also provides for a method of preventing metastasis of cancer to bone comprising administering a therapeutically effective amount of an OPG polypeptide.

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or treating a metastatic bone disease in a mammal comprising administering a therapeutically effective amount of an OPG polypeptide in combination with a cancer therapy agent. The cancer therapy agent may be any agent which is used to treat tumor growth including radiation therapy and chemotherapeutic drugs.

Examples of such agents include anthracyclines, taxol, tamoxifen, antibodies, such as anti-Her2 or anti-CD20 antibodies, and receptor agonists and antagonists, such as luteinizing hormone-releasing hormone (LHRH) antagonists. OPG polypeptide compositions may be administered prior to, concurrent with, or subsequent

to administration of a cancer therapy agent.

Figure 9 shows prevention of osteolytic bone destruction in C26-DCT and MDA-MB-231 models of tumor metastasis to bone. Both cells types produce localized bone destruction (yellow arrows) following inoculation directly into the left ventricle of mice. Panels on the. . .

Figures 11A and 11B show prevention and reversal of hypercalcemia associated with malignancy in a mouse C26-DCT tumor model. In the prevention study, met FcAC-OPG[22-1941 was given by daily subcutaneous injection. In the reversal study, met FcAC-OPG[22-194] was given by a. . .

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Detailed Descrilotion of the Invention

The present invention provides for compositions and methods for the prevention and treatment of bone loss associated with cancer. The present invention also provides for methods for the prevention and treatment of cancer using an anti-resorptive bone agent. Preferred compositions and methods of the invention include OPG and OPG fusion polypeptides. More particularly, the present invention relates to the use of OPG fusion protein compositions for the prevention and/or treatment of cancer or for the prevention and/or treatment of bone loss associated with cancer.

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the amino terminus (with or without a leader sequence) and/or the carboxy terminus, cleavage of a smaller polypeptide from a larger precursor, N-linked and/or 0-linked glycosylation, and the like.

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that have been chemically modified, as for example, by covalent attachment of one or more polymers, including, but limited to, water soluble polymers, N-linked or 0-linked carbohydrates, sugars, phosphates, and/or other such molecules. The derivatives are modified in a manner that is different from native Fc or OPG,. . .

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segments wherein the joined ends of the peptide or protein segments may be directly adjacent to each other or may be separated by linker or spacer moieties such as amino acid residues or other linking groups. A fusion may be accomplished by genetic or chemical means using procedures available to one skilled in the art although the. . .

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the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues may be divided into groups based on common side chain properties.

An Fc protein may be also linked to an OPG moiety of the OPG fusion polypeptide by spacer or linker moieties. Such spacers or linkers may be proteinaceous in that they comprise one or more amino acids or they may be chemical linkers. Such chemical

linkers are well known in the art. Amino acid linker sequences can include but are not limited to.

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comprising the OPG
truncated polypeptides described herein encompass joining of the OPG and heterologous peptide or polypeptide moieties directly or through a spacer or linker molecule wherein the spacer or linker optionally
comprises one or more amino acid residues. Variants and derivatives of the OPG truncated forms described herein are also encompassed by the. . .

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and the term FcGl(refers to an Fc moiety
- 18
lacking amino acid residues 1-9 inclusive, and having a ser- (gly) . linker.

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moiety
of a fusion protein. Also provided for are Fc or OPG variants comprising an addition and/or a deletion of one or more N-linked or O-linked glycosylation sites,
or comprising Fc or OPG polypeptide fragments as described above. It is understood that the nucleic acid molecules of the invention. . .

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fusion polypeptide may
not be biologically active upon isolation. various methods for refolding or converting the polypeptide to its tertiary structure and generating disulfide linkages, can be used to restore biological activity.

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particular redox potential allowing
for disulfide shuffling to occur in the formation of the protein's cysteine bridge(s). Some of the commonly used redox couples include cysteine/cystamine, glutathione (GSH)/dithiobis GSH, cupric chloride, dithiothreitol(DTT)/dithiane DTT, and 2-mercaptoethanol(PME)/dithio-P(ME). In many instances,.

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polymers. one skilled in the art will be able to select the desired polymer based on such considerations as whether the polymer/protein conjugate will be used therapeutically, and if so, the desired
5 dosage, circulation time, resistance to proteolysis, and other considerations. For the present proteins, the. . .

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of the protein. There
are a number of attachment methods available to those skilled in the art (EP 0401384 herein incorporated by reference (coupling PEG to G-CSF); Malik et al., Exp.

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of bone (osteitis deformans) in adults
and juveniles; osteomyelitis, or an infectious lesion in bone, leading to bone loss; Hypercalcemia resulting from solid tumors (breast, lung and kidney) and hematologic malignacies (multiple myeloma, lymphoma and leukemia), idiopathic hypercalcemia, and hypercalcemia associated with hyperthryoidism and renal function disorders; Osteopenia. . .

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half-life, are
advantageously used to treat bone loss, and especially bone loss resulting from osteolytic destruction of bone caused by malignant or metastatic tumors. OPG polypeptides of the invention may be used to treat bone loss associated with breast, prostate, thyroid, kidney, lung, esophogeal, rectal, bladder, cervical, ovarian and liver cancers as well as cancer of the gastrointestional tract. Also included is bone loss associated with certain hematological malignancies such as multiple myeloma and lymphomas such as Hodgkin's Disease.

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The OPG fusion proteins of the invention are administered alone or in combination with other therapeutic agents, in particular, in combination with other cancer therapy agents. Such agents generally include radiation therapy or chemotherapy.

Chemotherapy may involve treatment with one or more of the following: anthracyclines, taxol, tamoxifene, doxorubicin, 5-fluorouracil, and other drugs known to the skilled worker. In one embodiment, the cancer therapy agent is a luteinizing hormone-releasing hormone (LHRH) antagonist, preferably a peptide antagonist. More preferably, an LHRH antagonist is a decapeptide comprising the following structure.

In another embodiment, an LHRH antagonist comprises the peptide.

Nal 3-(2-napthyl)alaninyl
4-Cl-phe (41-chlorophenyl)alaninyl
Pal 3-(3'-pyridyl)alaninyl
Pal(N-0) 3-(3'-pyridine-N-oxide)alaninyl
iPr-LyS N-epsilon propyl-lysinyl
Qal 3-(21-quinolinyl)alaninyl
Alternative forms of LHRH antagonist decapeptides are also encompassed by the invention.

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such antibodies include those which bind to cell surface proteins Her2, CDC20, CDC33, mucin-like glycoprotein and epidermal growth factor receptor (EGFR) present on tumor cells and optionally induce a cytostatic and/or cytotoxic effect on tumor cells displaying these proteins. Examples of such antibodies include HERCEPTIN for treatment of breast cancer and RITUXAN for the treatment of non-Hodgkin's lymphoma. Also included as cancer therapy agents are polypeptides which selectively induce apoptosis in tumor cells, such as the TNF-related polypeptide TRAIL.

OPG fusion proteins may be administered prior to, concurrent with, or subsequent to treatment with a cancer therapy agent. OPG fusion proteins may be administered prophylactially to prevent or mitigate the onset of bone loss by metastatic cancer or may be given for the treatment of an existing condition of bone loss due to metastasis.

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and/or treat bone loss associated with multiple myeloma or to prevent and/or treat the disease itself. Multiple myeloma is a B cell

derived tumor that results in significant morbidity and mortality. The most striking common clinical manifestation is the focal bone loss due to increased osteoclast activation. . .

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in bone marrow spaces. The normal osteoclasts adjacent to the myeloma cell in turn produce IL-6, leading to local expansion of the tumor cells. Myeloma cells expand in a clonal fashion and occupy bone spaces that are being created by inappropriate bone resorption.

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treatment in myeloma patients would not only block the hyper resorption of bone, but could also affect the expansion and survival of the tumor itself. B-cells are known to express the receptor for OPGL, referred to as osteoclast differentiation and activation receptor, or ODAR.

Thus, OPG treatment could directly affect tumor cell survival, thus decreasing or eliminating, the tumor burden seen in myeloma patients.

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Delivery II, Keystone, Colorado, March, 1990 (recombinant human growth hormone); Debs et al., The Journal of Immunology 140: 3482-3488 (1988)(interferon - 42
a and tumor necrosis factor (X) and U.S. Patent No.

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nose,
without the necessity for deposition of the product in the lung. Formulations for nasal delivery include those with dextran or cyclodextran. Delivery via transport across other mucus membranes is also contemplated.

EXAMPLE 2
OPG Activity in a Breast Cancer model for Lytic Bone Disease
Female Balb/c nu/nu mice aged 7-8 weeks were injected with human MDA-MB-231 breast cancer cells (1.0 x 10' cells/mouse; ATCC accession no. HTB-26) directly into the systemic circulation via the left ventricle.

Immediately following tumor inoculation, the mice were treated by intravenous injection with either phosphate buffered saline (PBS) or met FcAC-OPG[22-1941 (25mg/kg) three times per week for. . . of lesions/mouse was assessed from radiographs. Bone, heart, lung, liver, kidneys, adrenals, ovaries, brain, pancreas and spleen were evaluated histologically for the presence of tumor foci as described below.

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a Mouse Adenocarcinoma Model for Lytic Bone Disease
Female CDF1 mice aged 7-8 weeks were injected with murine C26-DCT adenocarcinoma cells (obtained from the Tumor Repository of the National Cancer Institute;
1.0 x 10' cells/mouse) directly into the systemic circulation via the left ventricle. Immediately following tumor inoculation, mice were treated by intravenous injection with either PBS or met FcAC-OPG[22-1941 (25mg/kg) every 3 days for 9 days. On. . .

The C-26 tumor, originally induced in a female Balb/c mouse by repeated intrarectal instillation of N-nitroso-N-methylurethan (NMU) (Corbett et al. Cancer Res. 35, 2434-2439 (1975)), was obtained from the Tumor Repository of the National Cancer Institute in the form of tissue fragments. The fragments were mechanically disrupted and placed into culture under standard tissue culture conditions (37'C, 5-6%. . .

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were injected subcutaneously (SQ) over a shaved area of the right flank with 0.2 cc (0.5 x 10' cells) . Under these conditions tumor development was found to be very consistent with minimal variability.

In the treatment studies, met FcAC-OPG[22-194] was administered as a single intravenous injection in PBS vehicle. In both studies normal and tumor bearing control animals received a similar injection of PBS.

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bone analysis program (Osteometrics Inc., Decatur, GA). Two separate regions of the tibia were chosen for measurement so an accurate determination of the tumor induced increase in bone resorption could be obtained. The field of measurement consisted of a Imm x 1mm square area in both locations. . .

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on body weight loss. Mice receiving a daily 2.5mg/kg dose of OPG lost an average of 5.2 grams body weight while untreated tumor bearing animals lost an average of 6.2 grams. PBS tumor bearing mice had tumors that were 3.47 ± 0.72% vs OPG 2.5 mg/kg 3.42 + 0.82%. Weights are: PBS 0.75 ± 0.14g and OPG 2.5.

OPG -prevents and reverses C-26 tumor induced increases in blood ionized calcium levels

When treatment was commenced on day 9 following implantation of the tumor, OPG dose-dependently inhibited the increase in whole blood ionized calcium levels induced by the tumor (see Figure 11A). Prior to commencing OPG treatment, the tumor bearing mice had slightly increased whole blood ionized calcium levels (1.34 ± 0.06 mmol/L vs 1.25 + 0.02 mmol/L). In the vehicle treated. . .

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+ 0.06 mmol/L on dayl5 in the 2.5 mg/kg group. This level of calcium was moderately but significantly higher than that found in non-tumor bearing control animals. OPG treatment had no effect on calcium levels in non-tumor bearing mice.

OPG nrevents and reverses C-26 tumor induced increases in osteoclast lined bone surfaces and osteoclast numbers

Osteoclast lined surfaces and osteoclast numbers were markedly elevated in hypercalcemic mice bearing C26 tumors. Treatment with a 2.5 mg/kg dose of OPG either prior to or after the development of hypercalcemia caused almost a completed disappearance of osteoclasts. Osteoclast surface measurements, an

indication of the amount of bone resorption, were significantly increased in the tumor bearing animals, 8.95 ± 2.10%, compared to non tumor bearing controls 3.91 ± 1.10%. A 2.5 mg/kg dose of OPG given daily prior to the development of hypercalcemia dose dependently reduced these to 0.13 ± 0.07% which is significantly lower than even the non tumor bearing control animals.

The number of osteoclasts per mm bone surface were also elevated in the tumor bearing animals to 4.41 * 1.03 /mm compared to non tumor bearing controls 2.00 * 0.52 /mm. A daily 2.5 mg/kg dose of OPG dose dependently reduced the number of osteoclasts per mm to 0.12 ± 0.06 /mm which is significantly lower then even the non-tumor bearing animals.

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percent of bone surface measurements as well as the number of 5 osteoclasts per mm bone surface were both significantly elevated in the tumor bearing control animals 8.95 ± 1.64 % and 4.12 ± 0.72 osteoclasts per mm respectively, when compared to normal non-tumor bearing animals 3.66 + 1.01 % and 1.83 ± 0.54 osteoclasts per mm. A daily 2.5 mg/kg dose of OPG significantly reduced. . .

CLMEN 2 A method for preventing the metastasis of cancer to bone comprising administering a therapeutically effective amount of an OPG polypeptide.

4 The method of Claim I or 2 or 3 further comprising administering a therapeutically effective amount of a cancer therapy agent.

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of Claim 1 or 2 or 3 wherein the OPG polypeptide is administered prior to, concurrent with, or subsequent to administration of a cancer therapy agent.

13 The method of Claim 1 or 3 wherein lytic bone disease occurs in conjunction with cancer which has metastasized to bone.

14 The method of Claim 13 wherein the cancer is selected from the group consisting of breast cancer, prostate cancer, thyroid cancer, cancer of the kidney, lung cancer, esophogeal cancer, rectal cancer, bladder cancer, cervical cancer, ovarian cancer, liver cancer, cancer of the gastrointestinal tract, multiple myeloma, and lymphoma.

15 The method of Claim I or 2 or 3 wherein the cancer therapy agent is selected from the group consisting of radiation, chemotherapy, antibodies, or non-antibody polypeptides.

16 The method of Claim 15 wherein chemotherapy comprises anthracyclines, taxol, tamoxifene, doxorubicin, and 5-fluorouracil.

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of Claim 15 wherein the

antibodies bind to Her2, CDC20, CDC33, mucin-like glycoprotein, or epidermal growth factor receptor (EGFR) on the surface of tumor cells.

18 The method of Claim 15 wherein the cancer therapy agent comprises a luteinizing hormone-releasing
hormone (LHRH) antagonist.

19 The method of Claim 18 wherein the LHRH antagonist comprises the following structure:
A-B-C-D-E-F-G-H-I-j
wherein
A is pyro-glu, Ac-D-Nal, Ac-D-Qal; Ac-Sar, or Ac-D-Pal;
B is His or 4-Cl-D-Phe;
C is Trp, D-Pal, D-Nal, L-Nal-D-Pal(N-0),. . .

20 The method of Claim 18 wherein the LHRH antagonist comprises the peptide: N-Ac-D-Nal Cl-Phe-D-Pal-Ser-N-Me-Tyr-D-Asn-Leu-Lys(iPr)-Pro-D-Ala-NH2.

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